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TITLE: Do Black Men with Metastatic Castration-Resistant Prostate Cancer Have Worse Outcomes Than White Patients? A Nationwide VA Study

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14. ABSTRACT

Black men have a higher prostate cancer (PC) risk and mortality than white men. Whether these differences are due to lack of access to care or more aggressive biology is debated. However, a few small studies suggested black men may actually have better outcomes than white men when treated with metastatic castration-resistant PC (mCRPC) drugs. We hypothesize that black men with mCRPC will have similar responses to modern mCRPC therapies but worse compliance; after accounting for poorer compliance, black men will actually have better responses to these therapies than white men. Our objective is, to create a true nation-wide cohort from the Veterans Affairs (VA) Health System. Our preliminary analyses identified 46,535 men treated with one of 6 drugs for mCRPC (Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Radium-223, and Sipuleucel-T). We will 1. Determine drug efficacy among black and white men with mCRPC; 2. Determine drug compliance among black and white men with mCRPC; and 3. Determine drug efficacy among black and white men with mCRPC after accounting for compliance.

15. SUBJECT TERMS None listed.

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INTRODUCTION

Black men have a higher prostate cancer (PC) risk and mortality vs. white men. Whether these differences are due to lack of access to care or more aggressive biology is debated. In an equal access setting, we found black men had more PC, higher-grade PC, and more recurrences after surgery, arguing for more aggressive disease in black men. However, though we found recurrences after surgery were greater in black men, after adjusting for baseline disease differences, race was unrelated to recurrence or long-term outcomes (metastasis or PC death). Similarly, among men who failed surgery and received androgen deprivation therapy (ADT), long-term outcomes were unrelated to race (Vidal et al, Cancer 2019). This suggests, that when baseline differences are accounted for and men receive equal treatments, black men can experience similar outcomes as white men. Whether this is true for men with metastatic castration-resistant prostate cancer (mCRPC) receiving one of the new life-prolonging therapies is unknown. For the first time, we will test whether properly treated mCRPC black men have similar (or better) responses than white men. Importantly, understanding treatment patterns, efficacy, and adherence of life prolonging therapies for mCRPC by race is necessary not only to design rationale approaches to reducing PC health disparities, but also to help clinicians trying to decide the best drug to give to a man newly diagnosed with mCRPC based on race. To fulfill this goal, we are creating a true nation-wide cohort from the Veterans Affairs (VA) Health System. Our preliminary analyses identified 39,925 men treated with one of 6 drugs for mCRPC (Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Radium-223, and Sipuleucel-T).

KEYWORDS

Prostate cancer; metastatic castration-resistant prostate cancer (mCRPC); race; Veterans

ACCOMPLISHMENTS

What were the major goals of the project?

SOW Major Goals (as proposed in 2019):

STATEMENT OF WORK – 10/11/2018
PROPOSED START DATE October 1, 2019

Site 1: Cedars-Sinai Medical Ctr
8700 Beverly Blvd
Los Angeles 90048

Site 2: Durham VA
Durham, NC 27707

PI: Jun Gong (JG)
Co-I: Stephen Freedland

Specific Aim 1: Determine drug efficacy among black and white men with mCRPC	Timeline	Site 1	Site 2
Major Task 1: Data Collection & Preparation	Months		
Subtask 1: Abstract data of all men with mCRPC	1-12	Dr. Gong	Data Operations Manager, Michael Burns, under JG supervision
Subtask 2: Create a SQL server database, managed using Microsoft SQL Management Studio	1-12	Dr. Gong	Michael Burns, under JG supervision
Milestone Achieved: Preparation of large dataset including drugs used	1-12		

Major Task 2: Statistical Analysis			
Subtask 1: Conduct statistical analyses	13-23	Dr. Gong	Jessica Janes, under JG supervision
Subtask 2: Interpret results	13-23	Drs. Gong, Freedland	Drs. Freedland, Gong
Subtask 3: Archive datasets for future analyses and future patient follow-up.	18-23	Dr. Gong	Michael Burns
Milestone Achieved: Create the largest dataset on mCRPC by race. Manuscript preparation			

Aim 1: Determine drug efficacy among black and white men with mCRPC. We will use the largest integrated health system in the US: The Veterans Health Administration. We will retrieve data on mCRPC therapies including Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide to compare drug efficacy among black and white men. Too few men were treated with Radium-223 or Sipuleucel-T for analysis. Drug efficacy will be measured as PSA maximum decline. We hypothesize black and white men have similar responses to mCRPC therapies.

Major Task 1: 1-12 First Months (First Year Progress Report): Data collection and Preparation.

Major Task 2: 13-23 Months (Second Year Progress Report): Statistical Analysis.

What was accomplished under these goals?

1. **Major Activities – *Aim 1***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed for Aim 1, please see SOW for Aim 1 above. As the SOW indicates, in the first 12 months of this study we conducted Data Collection and Preparation for the study, a major, time-consuming work. Below we expand on the work completed so far:

a) Local Durham VA Health Care system IRB approval, as well as VA Informatics and Computing Infrastructure (VINCI) approval, have been obtained so that we may proceed with all study activities, with all personnel required to complete these tasks.

b) Data collection has been completed as concerns for the objectives of Aim 1, as planned in the SOW.

	Table 1. Number of Patients with mCRPC treated at the VA			
	No record or other race	**Black**	**White**	**Total x Treat**
Distinct Patients x Race	5,727	7,737	26,461	39,925
Number of Patients (Patients can be counted multiple times)				
Cabazitaxel	60	215	484	759
Docetaxel	4008	2818	13205	20031
Abiraterone	1276	2822	9768	13866
Enzalutamide	812	2054	6812	9678

Table 1 shows the preliminary numbers of all men available to us within VINCI, reflecting treatment for mCRPC at National VA centers, since January 1, 2000. The data queries developed for mCRPC drugs resulted in a dataset of 39,925 men; of these, 11,474 received first treatment of Abiraterone; 20,201 with Docetaxel; and 5,136 with Enzalutamide. As we anticipate that the majority of mCRPC men receiving therapy within the VA system are regular users, these 39,925 men will be our analytic cohort and represents the largest cohort ever studied for mCRPC health disparities.

This cohort was initially identified using prostate cancer diagnosis ICD codes. Patients with a prostate cancer diagnosis code were then evaluated for metastatic, castrate-resistant disease based on a series of queries that classify a patient as (1) metastatic, (2) castrate, and/or (3) castrate resistant. Castrate resistance is determined by comprehensively evaluating hormone therapy treatment cycles and/or an orchiectomy procedure in conjunction with PSA lab results.

Patients who received abiraterone and/or enzalutamide treatments were classified as mCRPC patients. Patients identified as mCPRC were further evaluated for receipt of cabazitaxel and/or docetaxel treatments.

Treatments were identified using a combination of CPT codes and pharmacy data.

c) In addition to the queries developed to determine the data in Table 1, queries have been developed to determine information across a variety of our data elements of interest, notably for: demographic data, including race and age; and certain lab(s)/lab results, including prostate specific antigen (PSA), variables that will be used in the statistical analysis.

d) The NLP race model our team developed for this project, is a regular expression, race classifier paradigm utilizing a majority vote approach to output final results; this strategy has been adopted because within an individual patient there may exist n number of provider notes, each of which may have race reported differently, dependent upon a variety of factors. In addition to the race model, a prostate cancer metastasis model has also been generated, trained, and developed, and which employs a binomial (positive, negative) logistic regression paradigm. This logistic regression model uses keywords and keyword modifiers, extracted through provider and scan/radiology note sentence parsing to then assign a classification of “positive” or “negative” scan.

Site 1: Cedars-Sinai Medical Ctr
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PI: Jun Gong

Site 2: Durham VA
Durham, NC 27707
PI: Jun Gong (JG)
Co-I: Stephen Freedland

Specific Aim 2: Determine drug compliance among black and white men with mCRPC			
Major Task 1: Prepare data for analysis drug compliance by race			
Subtask 1: Retrieve data on compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration. We will also determine whether the duration of drug therapy and time until next therapy differs between black and white men.	6-12	Dr. Gong	Data Operations Manager, Michael Burns, under JG supervision
Subtask 2: Analyze data on whether drug compliance differs by race	13-24	Drs. Gong, Freedland	Jessica Janes, under JG supervision
Milestone(s) Achieved: Largest study ever to address drug compliance for mCRPC by race			
Specific Aim 3: Determine drug efficacy among black and white men with mCRPC after accounting for compliance.			
Major Task 1: Prepare data for analysis			
Subtask 1: Ascertain response to drug, measured as PSA maximum decline, after accounting for compliance. Subtask 2: Analyze data and adjust for potential confounders including age, comorbidities, socioeconomic status, VA center, but also Gleason score, and primary treatment received	10-14 14-24	Dr. Gong Freedland Dr. Gong Freedland	Drs. Freedland, Gong Jessica Janes, under Drs. Freedland, Gong supervision
Milestone(s) Achieved: Determine drug efficacy for mCRPC by race in the largest dataset ever created.			

Aim 2: Determine drug compliance among black and white men with mCRPC. Among men given a mCRPC life-prolonging drug, we will determine compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration. We will also determine whether the duration of drug therapy and time until next therapy differs between black and white men. We hypothesize black men have reduced compliance to mCRPC therapies vs. white men.

Major Task 1:
Subtask 1: 1-6 Months (First Year Progress Report): Prepare data for analysis on drug compliance by race
Subtask 2: 13-23 Months (Second Year Progress Report): Statistical Analysis

1. **Major Activities – *Aim 2:***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed to conduct in the first year of the award for Aim 2, as detailed in SOW above. As the SOW indicates, in the first 6 months of this study we conducted Data Preparation for analysis on drug compliance by race, a major, time-consuming work. Below we expand on the work completed so far:

a) We have retrieved data on compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration.

b) We have calculated the duration of drug therapy and time until next therapy in each race group.

Aim 3: Determine drug efficacy among black and white men with mCRPC after accounting for compliance. Among the men described in Aims 1 and 2, we will analyze response to drug, measured as PSA maximum decline, *after* accounting for compliance. We hypothesize response to therapy after accounting for compliance, is better in black men compared to white men.

Major Task 1:

Subtask 1: 10-14 Months (First Year Progress Report): Prepare data for analysis

Subtask 2: 14-24 Months (Second Year Progress Report): Statistical Analysis

1. **Major Activities – *Aim 3:***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed for Aim 3, as detailed in SOW for Aim 3 above. As the SOW indicates, in the first 14 months of this study we ascertained response to drug, measured as PSA maximum decline, after accounting for compliance. Below we expand on the work completed so far:

a) We determined the percent of patients experiencing a $\geq$ 30% maximum decline in PSA, a level that approaches surrogacy for explaining the survival benefits of androgen receptor (AR) targeted therapy and had a high degree of surrogacy for docetaxel treated patients.

2. **Specific Objectives – *Aims 1-3:***

The specific objectives for Aims 1-3 were to obtain all the data and create the database to conduct analysis. As described in Major Activities for Aim 1, we collected and prepared the data needed for the analysis of determining drug efficacy among black and white men with mCRPC; for Aim 2, we collected the data on compliance, the duration of drug therapy and time until next therapy in each race group; for Aim 3, we collected data on drug response by race group.

3. **Significant Results - *Aims 1-3:***

We have achieved significant results as scheduled in the SOW timeline, i.e. we have collected all data as expected. However, at this point, a comprehensive dataset has not been finalized. As stated in the SOW, we anticipate to conducting statistical analyses during the following year of this award.

4. **Other achievements:**

A new study coordinator and statistician have been on-boarded to the team at the Durham VA, to help us with this study and keep moving the project forward as planned.

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

A new study coordinator, **Joshua Parrish**, has been on-boarded to the study team. He has been learning in-depth clinical prostate cancer knowledge and is learning about the VA's national data system (VINCI & CDW). He has received formal leadership coaching in his role.
Ruixin Yang, our data scientist, has been developing a manuscript for peer review describing one of the machine learning models being used in this study. He is working under the guidance of Dr. Klaassen, a VA urologist.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

Our next step will be to apply the queries and NLP models above-mentioned to the study cohort, to develop a comprehensive dataset. This is a computationally intensive process given the size of the cohort (~40,000 men) and complexity of the data returned, which will require considerable quality assurance. Once the dataset is generated, the PI and statistician will perform quality assurance measures and begin analysis. We anticipate the statistical analysis will be conducted well before the end of the following year of this grant.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

As we have not finished analyzing the data, no impact on society has yet been achieved. However, we expect our results will impact the treatment of advanced-stage prostate cancer, specifically mCRPC for black Veterans.

Thus, nothing to report at this time.

CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to Report.

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

Within the prior year we have been forced to delay work on this project due to a required change in PI. This recent change in PI to Dr. Jun Gong has now been completed. While awaiting this change we have not completed any further work in the past few months after initial cohort identification and data queries and plan to resume analyses promptly in the coming year.

Changes that had a significant impact on expenditures

N/A

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

N/A

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

PRODUCTS

- **Publications, conference papers, and presentations**

Journal publications.

The manuscripts listed below are related to this project, however, not directly funded with this DoD award. These studies, from our group, helped move the field forward in terms of mCRPC and racial disparities, the main topic of this award. Thus, this is why I have decided to include them in this report.

1. Validation of a genomic classifier for prediction of metastasis and prostate cancer-specific mortality in African-American men following radical prostatectomy in an equal access healthcare setting. Howard LE, Zhang J, Fishbane N, Hoedt AM, Klaassen Z, Spratt DE, Vidal AC, Lin D, Hitchins MP, You S, Freeman MR, Yamoah K, Davicioni E, **Freedland SJ**. Prostate Cancer Prostatic Dis. 2019 Dec 16. doi: 10.1038/s41391-019-0197-3. Online ahead of print. PMID: 31844180.
2. Racial Discrepancies in Overall Survival among Men Treated with ^{223}Radium. Zhao H, Howard LE, De Hoedt A, Terris MK, Amling CL, Kane CJ, Cooperberg MR, Aronson WJ, Klaassen Z, Polascik TJ, Vidal AC, **Freedland SJ.** J Urol. 2020 Feb;203(2):331-337. doi: 10.1097/JU.0000000000000524. Epub 2019 Sep 3. PMID: 31479407

Books or other non-periodical, one-time publications.

N/A

Other publications, conference papers and presentations.

N/A

- **Website(s) or other Internet site(s)**

N/A

- **Technologies or techniques**
  N/A

- **Inventions, patent applications, and/or licenses**
  N/A

- **Other Products**
  N/A

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project? Site I

No change

Name: *Jun Gong*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: ***0.36***
Contribution to Project: *Leads the project*
Funding Support:
Name: *Marcio Diniz*
Project Role: *Biostatistician*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: ***0.24***
Contribution to Project: *Power calculations*
Funding Support:
Name: *Stephen Freedland*
Project Role: *Co-Investigator*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: ***0.12***
Contribution to Project: *Guidance and expertise*
Funding Support:

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

What other organizations were involved as partners? (Subcontract, Site 2)

Organization Name: Durham VA Health Care System (DVAHCS)/Institute for Medical Research (IMR)
Location of Organization: Durham, North Carolina
Partner's contribution to the project: The team at DVAHCS/IMR provides database development, protocol/regulatory, and data analysis support.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

APPENDICES