

**The YODA Project
Research Proposal Review**

The following page contains the final YODA Project review
approving this proposal.

The YODA Project
Research Proposal Review - Final
(Protocol #: 2022-5030)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross
- Joshua Wallach

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | Yes |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Approve |

Comments:

No additional comments

**The YODA Project
Research Proposal Review**

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and
the original submitted proposal.

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2022-5030)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross
- Joshua Wallach

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | No |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Not Approve |

Comments:

1. The term "Asian" is an ambivalent form of self-identification which is used differently in different countries. In the US, "Asian" is used most frequently to describe people of Chinese, Japanese or other Far Eastern origin. In the UK it is used mostly to describe people from the Indian subcontinent. How do you propose to check for ethnicity at a more accurate level which might better reflect genetic differences in response?
2. Is there a reason of choosing "Asian" as the term of interest without including other ethnic descriptors in the analysis (e.g. Black, Hispanic etc)?

Principal Investigator

First Name: Yao
Last Name: Zhu
Degree: MD
Primary Affiliation: Fudan University Shanghai Cancer Center
E-mail: xdni18@fudan.edu.cn
Phone number:
Address: dongan road

City: Shanghai
State or Province: Shanghai
Zip or Postal Code: 200032
Country: China
SCOPUS ID: 22955119300

General Information

Key Personnel (in addition to PI):
First Name: Yao
Last name: Zhu
Degree: MD
Primary Affiliation: Fudan University Shanghai Cancer Center
SCOPUS ID: 22955119300

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

<https://yoda.yale.edu/system/files/coizy.pdf>

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00638690 - COU-AA-301 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy](#)
2. [NCT00887198 - COU-AA-302 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer](#)
3. [NCT01695135 - ABI-PRO-3001 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(JNJ-212082\) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy](#)
4. [NCT01591122 - ABI-PRO-3002 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(JNJ-212082\) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With](#)

[Metastatic Castration-Resistant Prostate Cancer](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Overall Survival and Radiographic Progression Free Survival difference between Asian and White mCRPC patients treated with Abiraterone

Narrative Summary:

In patients with metastatic castration-resistant prostate cancer (mCRPC), there may be differences in the sensitivity of Asians and Whites to various treatments. This difference will be reflected in the overall survival (OS) and radiographic progress free survival (rPFS). We hope to determine the differences in OS and rPFS between Asian mCRPC patients and white under the same treatment conditions by analyzing these four clinical trials, and further analyze the deep-seated reasons for the differences. So as to provide a factual basis for the study of the genetic basis of treatment sensitivity in different races and the necessity of including different races in future clinical trials.

Scientific Abstract:

Background?

Prostate cancer (PCa) is the second most commonly diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide, with an estimated 1,414,259 new cancer cases and 375,304 deaths in 2020[1]. Although Asian has a relatively lower incidence and mortality rate than White[2], data on racial disparities in men with advanced prostate cancer are limited[3-4]. Furthermore, In multi-center clinical trials for prostate cancer, Asian is always under-represented[5]. As Abiraterone has become a standardized treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), we hypothesized that Asian and White may have difference in overall survival (OS) and radiographic progress free survival (rPFS) after treated with Abiraterone.

Objective?

Using individual patient data from NCT00638690, NCT01695135, NCT00887198, NCT01591122 these four clinical trials which including mCRPC patients treated with Abiraterone to perform race-stratified (Asian vs. White) analysis for OS and PFS survival.

Study Design?

A post-hoc analysis of NCT00638690, NCT01695135, NCT00887198, NCT01591122 will be performed to estimate the distribution of outcomes according to patients' geographic locations. Compare the sensitivity difference to Abiraterone between Asian and White.

Participants?

Patients enrolled in NCT00638690, NCT01695135, NCT00887198, NCT01591122 trials treated with Abiraterone. Patients treated with placebo will be used as a reference.

Primary and Secondary Outcome Measure(s)?

Overall survival & Radiographic progression free survival

Statistical Analysis?

R Statistical software will be used for all assessments. Baseline data of patients (Asian vs. White) will be first balanced by Propensity Score Matching (PSM) and then estimated by Kaplan-Meier analysis, with hazard ratios calculated using a multivariate Cox proportional-hazard model.

Brief Project Background and Statement of Project Significance:

Prostate cancer (PCa) is the second most commonly diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide, with an estimated 1,414,259 new cancer cases and 375,304 deaths in 2020[1]. Although Asian has a relatively lower incidence and mortality rate than White[2], data on racial disparities in men with advanced prostate cancer are limited[3-4]. Furthermore, In multi-center clinical trials for prostate cancer, Asian is always under-represented[5]. As Abiraterone has become a standardized treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), we hypothesized that Asian and White may have difference in overall survival (OS) and progress free survival (PFS) after treated with Abiraterone.

All the four clinical trails in this application include “Abiraterone-prednisone” group and “placebo- prednisone” group. Among them, NCT00638690 mainly included white patients with mCRPC who have failed Docetaxel-Based Chemotherapy, NCT01695135 mainly included Asian patients with mCRPC who have failed Docetaxel-Based Chemotherapy, NCT00887198 mainly included white patients with mCRPC and no prior chemotherapy, NCT01591122 mainly included Asian patients with mCRPC and no prior chemotherapy. Therefore, to test our hypothesis, we will combine NCT00638690 trial with NCT01695135 trail and combine NCT00887198 with NCT01591122 to ensure the Asian and white patients enrolled have received the same treatment.

Our study, although hypothesis generating, may advance our understanding the disparity of mCRPC between the East and West. Besides, our study will provide a factual basis for the further exploration of the genetic basis of Abiraterone sensitivity in different races and the necessity of including different races in future clinical trials.

Specific Aims of the Project:

Objective: Using individual patient data from NCT00638690, NCT01695135, NCT00887198, NCT01591122 these four clinical trials which including mCRPC patients treated with Abiraterone to perform race-stratified (Asian vs. White) analysis for OS and PFS survival.

Hypothesis: Asian and White mCRPC patients may have difference in overall survival (OS) and progress free survival (PFS) after treated with Abiraterone.

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research on comparison group

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

We have identified 4 clinical trials that tested the treatment effect of Abiraterone in men with mCRPC. Among these 4 trials, NCT01695135 mainly included Asian patients with mCRPC who have failed Docetaxel-Based Chemotherapy, NCT00887198 mainly included white patients with mCRPC and no prior chemotherapy, NCT01591122 mainly included Asian patients with mCRPC and no prior chemotherapy. Patients in all these trials had histologically or cytologically confirmed prostate cancer and were considered to have disease progression. All the Asian and White patients from these 4 trails will be included. Meanwhile, patients whose baseline information or outcomes were incomplete will be excluded.

Other data source include SEER database will be used to confirm the outcome after analyzing above 4 clinical trials. Participant-level data from SEER will be processed on our own computer.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary end points include overall survival and radiographic progression-free survival in Asian and White with metastatic castration-resistant prostate cancer after treated with Abiraterone.

Secondary end points include PSA response and safety.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Race (Asian vs. White), Clinicopathological variables as age, body mass index, Gleason score, tumor stage, performance of status, site of metastases, PSA, medication, comorbidity, et al.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Race (White, African American, Asian, other)

Statistical Analysis Plan:

Participants who had the same treatment will be divided by race (Asian or White). Propensity score methods (PSM) will be used to balance the baseline differences between Asian and White. PSM will be performed by MatchIt package in Rstudio. Base on the data after PSM, Kaplan-Meier analysis and established multivariate Cox proportional-hazard model will be performed by survival and survminer package.

Software Used:

RStudio

Project Timeline:

We anticipated start the project In September this year, finish the analysis before 1 Sep 2023, and draft the manuscript for submission before 1 Mar 2024.

Dissemination Plan:

We plan to submit the project to well-known meetings (GU-ASCO, ESMO) and journals (European Urology, Annals of Oncology)

Bibliography:

- 1.Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021 May;71(3):209-249.
- 2.Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022 Jan;72(1):7-33.
- 3.Halabi S, Small EJ, Vogelzang NJ, Barrier RC Jr, George SL, Gilligan TD. Impact of race on survival in men with metastatic hormone-refractory prostate cancer. *Urology.* 2004 Aug;64(2):212-7.
- 4.Halabi S, Vogelzang NJ, Ou SS, Kelly WK, Small EJ. Clinical outcomes by age in men with hormone refractory prostate cancer: a pooled analysis of 8 Cancer and Leukemia Group B (CALGB) studies. *J Urol.* 2006 Jul;176(1):81-6.
- 5.Owens-Walton J, Williams C, Rompré-Brodeur A, Pinto PA, Ball MW. Minority Enrollment in Phase II and III Clinical Trials in Urologic Oncology. *J Clin Oncol.* 2022 May 10;40(14):1583-1589.