The YODA Project
Research Proposal Review

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

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2022-5106)

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 Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2022-5106)

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. It is unclear how the primary independent variable, Androgen indifferent prostate cancer, will be defined at baseline in the study cohort.
2. There seems to be missing text at the end of the section Brief Project Background and Statement of Project Significance.

Principal Investigator

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Country: Italia

General Information

Key Personnel (in addition to PI):
First Name: Alberto
Last name: Martini
Degree: MD
Primary Affiliation: University of Texas, MD Anderson Cancer Center
SCOPUS ID: 57162296600

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?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/coi_robesti_daniele.pdf
https://yoda.yale.edu/system/files/sv_6m4tghhxg7w7uxe-r_yvobfujlmgogruf.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. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant Prostate Cancer

5. NCT01795703 - JNJ-212082-JPN-202 - A Phase II Study of JNJ-212082 (Abiraterone Acetate) in Metastatic Castration-Resistant Prostate Cancer Patients Who Have Received Docetaxel-based Chemotherapy
6. NCT01867710 - 212082PCR2023 - A Randomized Phase 2 Study Evaluating Abiraterone Acetate With Different Steroid Regimens for Preventing Symptoms Associated With Mineralocorticoid Excess in Asymptomatic, Chemotherapy-naïve and Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients
7. NCT01715285 - 212082PCR3011 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)
8. 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
9. NCT02257736 - 56021927PCR3001 - A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC)

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

Research Proposal

Project Title

Assessing the Aggressive Variant Prostate Cancer patients reponse to novel antiandrogen-based regimen or taxanes.

Narrative Summary:

Novel antiandrogen therapies have challenged the perception that most men with prostate cancer uniformly benefit from androgen ablation. The diverse responses to these recently approved therapies with distinct mechanisms of action (e.g., second-generation androgen or biosynthesis inhibitors) have exposed the biological heterogeneity of prostate cancer and illustrate the need to apply our understanding of prostate biology to clinical decisions. We would like to assess whether the clinical criteria of Aggressive Variant Prostate Cancer, a clinical entity that is considered androgen indifferent, truly identify poor responders to abiraterone, novel antiandrogen, or their combination.

Scientific Abstract:

Background: the oncological outcomes of mCRPC patients are still heterogeneous. The diverse responses of Androgen Receptor targeting agents (e.g., second-generation androgen receptor inhibitors or biosynthesis inhibitors) illustrate the urgent need to apply the understanding of prostate cancer biology to clinical decision-making. To overcome this unmet need, some authors introduced the concept of Androgen indifferent prostate cancer (AIPC) variants, an umbrella term including aggressive variant prostate cancer (AVPC), neuroendocrine prostate cancer (NEPC), and double negative prostate cancer (DNPC), based on clinical and pathological features. These clinical criteria have not been implemented in clinical trial inclusion criteria yet.
Objective: to explore whether these clinical criteria truly identify patients not responding to novel antiandrogen therapies (ARTAs) and their combinations
Study design: a pooled analysis of randomized clinical trials and prospective cohorts of mCRPC patients.
Participants: mCRPC patients
Primary and Secondary outcomes: progression-free survival (PFS) overall survival (OS) and cancer-specific survival (CSS) and other cause mortality (OCM) of mCRPC patients.
Statistical analysis: based on the definition of AIPC, the whole population will be split into two groups. Multivariable cox regression analysis will test the association of AIPC status with oncological outcomes, namely PFS, and OS. The Gray test will be employed to test the equality of the cumulative incidence functions in the presence of

competing events Moreover, for those patients defined as AIPC, a comparison of different treatment regimens will be performed using multivariate cox regression analysis. Similarly, we will rely on the competing risks method to display the cumulative incidence functions for CSS and other causes of mortality (OCM) rates for the two aforementioned groups. Finally, if the AIPC clinical criteria fail to identify poor responders to ARTAs and their combinations, an analysis of intermediate clinical endpoints (ICE) will be performed according to Prentice Criteria.

Brief Project Background and Statement of Project Significance:

The recent development of novel antiandrogen therapies has challenged the perception that most men with prostate cancer benefit from androgen ablation uniformly. The diverse responses to these recently approved therapies with distinct mechanisms of action (e.g., second-generation androgen biosynthesis inhibitors) have exposed the biological heterogeneity of prostate cancer and illustrate the urgent need to apply our understanding of prostate cancer biology to clinical decision-making. To overcome this unmet need, some authors introduced the concept of Androgen indifferent prostate cancer (AIPC) variants, an umbrella term including aggressive variant prostate cancer (AVPC), neuroendocrine prostate cancer (NEPC), and double negative prostate cancer (DNPC). Often the clinical criteria defining these entities show some degree of overlapping, resulting in these phenotypes being ill-defined. Yet, these androgen-independent variants are associated with poor outcomes. Given the treatment intensification trend in PCA, they are becoming increasingly common clinically meaningful entities.
The investigators will explore whether these clinical criteria truly identify patients not responding to novel antiandrogen therapies (ARTAs) and their combinations, sparing patients from potential side effects related to their use, such as major cardiac events (MACES). Moreover, a comparison of the oncological outcomes of AIPC patients receiving other chemo-hormonal regimens will be carried out.
The results of our work may affect clinical trial inclusion criteria, sparing AIPC from receiving AR targeting agents. Moreover, the identification

Specific Aims of the Project:

The investigator seeks to analyze whether Androgen indifferent prostate cancer (AIPC) clinical criteria identify patients not responding to novel antiandrogen therapies (ARTAs) and their combinations. Moreover, a comparison with other treatment regimens will be carried out. So far, no study has evaluated the best treatment regimen for these patients. If these criteria fail to identify poor responders, an analysis of intermediate clinical endpoints (ICEs) in mCRPC will be carried out.

What is your Study Design?:

Other

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

Confirm or validate previously conducted research on treatment effectiveness

Preliminary research to be used as part of a grant proposal

Research on comparison group

Research on clinical prediction or risk prediction

Research Methods

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

INCLUSION CRITERIA:

- mCRCP patients
- age >18 yo

EXCLUSION CRITERIA
- none

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

The specific outcomes are:
- Overall survival
- Disease-specific survival
- Progression free survival
- Other cause mortality rate
- Major Cardiac Adverse events rate

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

The independent variable that will be investigated will be:
- Androgen indifferent prostate cancer (AIPC) status (yes vs.no)

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

Age, ethnicity, type of prior treatment, M status at diagnosis (M0 vs M1a vs M1b vs M1c), metastatic sites, time from ADT to mCRPC status, serum PSA at diagnosis, serum PSA at the start of treatment, for M+ disease burden at diagnosis (low volume vs high volume), lytic bone metastasis (yes vs no, if available, neuroendocrine biomarkers status (if available), bulky lymphadenopathy (?5 cm) or bulky high-grade mass (?5 cm, Gleason ?8) in the prostate or pelvis (yes vs no), serum CEA and/or LDH concentrarion (if available), neuroendocrine prostate cancer histology (yes vs mixed vs no), concurrent treatment at the time of diagnosis, previous treatment for prostate cancer, ECOG performance status, treatment regimen (ARTA vs ARTAs combination vs Taxanes), major cardiac events (MACEs) rate after mCRPC treatment initiation, time to major cardiac events, family history of prostate cancer (yes vs no) and the number of relatives, family history of other malignancy, p53, pRB, PTEN mutation status.

Statistical Analysis Plan:

The investigator seeks to analyze the impact of Androgen indifferent prostate cancer (AIPC) status on survival outcomes, namely overall survival and progression-free survival by means of the Cox regression or the Fine and Gray regression, if data on cancer specific mortality and other cause mortality is available, according to ARTAs-based treatment or chemotherapy regimens. Survival curves will be plotted according to the Kaplan-Meier method for overall survival and to the competing risks method for cancer specific mortality, if available. Moreover, intermediate clinical endpoints (ICEs) will be investigated, according to Prentice Criteria. Multivariable Cox regression analyses will be exploited to predict overall survival at different landmark points to evaluate the impact of the different intermediate endpoints.
Data on comorbidities, medical therapies at the time of randomization, survival and response outcomes will be necessary to carry out the proposed study.
Software Used:
RStudio
Project Timeline:

12 months

Dissemination Plan:

The study will be submitted to peer-reviewed journals for publication. Ideally on The Lancet Oncology or JAMA Oncology

Bibliography:

Berchuck et al. Prostate Cancer Prostatic Dis. 2021 September