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)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2017-1356)

Reviewers:

- ☒ Nihar Desai
- ☐ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross

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)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2017-1356)

Reviewers:

- ☒ Nihar Desai
- ☐ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross

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:

The authors should closely review their submission - there were several grammatical errors and typos that should be corrected, some of which obscured the clarity of the writing (for instance, "In this study, we will not focus on one several predictors.").

The 'Main Predictor/Independent Variable', 'Other Variables of Interest' and 'Statistical Analysis Plan' sections do not seem to reflect the stated purpose of the study: to examine the association between patient BMI and efficacy of abiraterone acetate. I expected the entirety of the 'Main Predictor/Independent Variable' section to be about BMI and how it would be treated as a variable (continuous? categorized? how?). Similarly, I expected the 'Other Variables of Interest' section to list all the other variables that would be used for risk-adjustment (and how they would be treated as variables).

The 'Statistical Analysis Plan' section makes no mention of examining associations with BMI nor risk-adjustment. Please clarify.

This a simple analysis which is probably worth doing, though not for the reasons given. By the time the participants have metastatic cancer and have received other forms of androgen deprivation therapy, chemotherapy or corticosteroids, their BMI may have changed greatly from the time of onset of their cancer, so the mechanistic justification for the analysis does not hold. It is unlikely that the data set will contain any information about BMI at the time of initial diagnosis.

Principal Investigator

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2017-1356

General Information

Key Personnel (in addition to PI): **First Name:** kun
Last name: chang
Degree: MD
Primary Affiliation: Fudan University, Shanghai, China
SCOPUS ID: 55816587400

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?: Colleague

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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

Associated Trial(s): NCT00638690 - 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
NCT00887198 - 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
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Does Body Mass Index predict efficacy of abiraterone acetate therapy in patients with metastatic castration-resistant prostate cancer?

Narrative Summary:
Recent studies have found that risk varies by stage of disease, tumor grade, and cause-specific mortality. Several meta-analyses have indicated that greater body mass index (BMI) is associated with increased risks of aggressive/advanced prostate cancer and prostate cancer– specific mortality, but the relationships for BMI and efficacy of abiraterone acetate therapy remain inconclusive. The aim of this study is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify the relationship between BMI and efficacy of abiraterone acetate. The results may help establish an economical and accessible biomarker to predict the efficacy of abiraterone.

Scientific Abstract:
Background: The increase in prostate cancer incidence and mortality observed in immigrants from low-risk to high-risk countries suggests that lifestyle and dietary factors play an important role in the etiology of prostate cancer. Excess body weight comprehensively reflects lifestyle and dietary factors, which occurs when the expenditure (i.e., physical activity) is less than the intake (i.e., high-fat diets).[1-3] Excess body weight, as measured by BMI, has been considered a factor for decreased and increased risk of localized and advanced prostate cancer, respectively. However, the relationship between BMI and efficacy of abiraterone acetate therapy remains unclear.
Objective: The objective of this study is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify whether BMI could provide some indication of efficacy of abiraterone acetate.
Study Design: Retrospective cohort study.
Participants: mCRPC patients from COU-AA-302 and COU-AA-301 treated with abiraterone or placebo.
Main Outcome Measures(s): Outcomes evaluated will include PSA progression-free survival, overall survival, progression free survival as well as response to subsequent therapies.
Statistical Analysis: Cox regression analysis will evaluate the role of BMI as a prognostic biomarker. Analyses will be stratified by treatment received, ECOG status, LDH, hemoglobin level, Gleason score, TNM stage and age, et al.

Brief Project Background and Statement of Project Significance:
Excess body weight, as measured by BMI, has been considered a factor for decreased and increased risk of advanced prostate cancer. There is a complex array of biological mechanisms through which obesity may influence prostate carcinogenesis and metastasis, including hyperinsulinemia, elevated insulin-like growth factor (IGF) hormone levels, dysregulation of sex steroid hormones, altered levels of adipokines, and chronic inflammation.[4-6] Obesity is also associated with chronic inflammation and biomarkers of inflammation in the body, such as higher levels of C-reactive protein, which have been associated with prostate cancer–specific mortality. [7,8] Obese men have been shown to exhibit reduced levels of androgens, and there is evidence that men with lower levels of testosterone have more aggressive tumors at clinical presentation.
Abiraterone functions by interference with steroid metabolism . Normally in the adrenal glands, adrenocorticotropic hormone (ACTH) stimulates metabolism of the steroid precursor pregnenolone. Pregnenolone can be further metabolized to aldosterone or to 17OH-pregnenolone, a common precursor for cortisol and testosterone. The action of 17[alpha]-hydroxylase converts pregnenolone to 17OH-pregnenolone, and 17,20-lyase further converts this product to dehydroepiandrostenedione (DHEA). DHEA is subsequently converted to an intermediary and finally testosterone. Abiraterone is a potent inhibitor of the 17[alpha]-hydroxylase and 17,20-lyase enzymatic functions of CYP17.[9] Recent preclinical work has also identified [DELTA]4-abiraterone, an active metabolite of abiraterone, that further inhibits 3[beta]-hydroxy steroid dehydrogenase, CYP17A1, and 5[alpha]-reductase. In the presence of ACTH stimulation and abiraterone, pregnenolone is shunted to mineralocorticoid synthesis. Abiraterone used without replacement corticosteroids to suppress ACTH results in a syndrome of mineralocorticoid excess.[10] Abiraterone thus was studied in conjunction with corticosteroids in its clinical development.
As a result, we supposed that excess body weight, as measured by BMI, may lead to the treatment resistance to the abiraterone of prostate cancer.

Specific Aims of the Project:

The objective of this study is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify whether BMI could act as a predictor of the efficacy of abiraterone acetate reffering to progression-free survival and overall survival.
Hypothesis: We supposed that excess body weight, as measured by BMI, may lead to the treatment resistance to the abiraterone of prostate cancer.

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

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Data source: COU-AA-302 and COU-AA-301
Inclusion criteria: all patients in the trial
Exclusion criteria: missing data

Main Outcome Measure and how it will be categorized/defined for your study:
Date of death (overall survival)
Date of PSA progression (PSA progression-free survival)
Date of Radiographic PFS (Radiographic progression-free survival)

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
In this study, we will not focus on one several predictors. We seek to investigate the variables associated with all cause mortality and disease progression. The variables of interest include:

Age at study entry (continuous)
Race
Treatment Arm (Abiraterone or placebo)
Gleason Score (Ordinal)
Date of Diagnosis
Body Mass Index (continuous)
Presence of liver metastases* (Present/Absent)
Presence of bone metastases (Present/absent)
Presence of nodal metastases (Present/absent)
Presence of visceral metastases (Present/absent)
Time from start of initial LHRH to abiraterone treatment* (continuous)
Weight (kg, each visit record from inclusion to the end of follow-up)
Prior anti-cancer therapies (number of prior hormonal therapies, prior ketoconazole, prior chemotherapies(COU-AA-302))
Prior prostatectomy and/or radiation therapy (Y/N for each)
Investigations (PSA, Hgb, Cr, AlkPhos, LDH)
Pain score / presence of pain (binary Y/N)
Performance Status (ECOG)
Mode of progression (clinical, radiographic, toxicity)
Best PSA response (% reduction)
Date of Abiraterone or Prednisone initiation
Adverse events or complications occurred during the treatment

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

Statistical Analysis Plan:
All analyses will be stratified by treatment group (abiraterone vs placebo) .Disease characteristics will be compared using descriptive statistics. Overall suvival and progression-free survival will be calculated by the Kaplan–Meier method with the log-rank test to assess differences between groups. Univariate and multivariate analysis of prognostic factors will be done using the Cox proportional hazard model. All statistical tests will be done using R

statistics package, version 2.8.1(http://www.r-project.org/).

Project Timeline:
Project start date: 2/2017
Analysis completion date: 3/2017
Date manuscript drafted/submitted: 4/2017
Results reported 7/2017

Dissemination Plan:
We plan to publish the results of this project in the form of a manuscript in oncology and urology medical journals.

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