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 #: 2017-2036)

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:

The investigators have provided a clear response to the questions raised, which when coupled with their request provides clear justification for the use of the data and the expectations for the scientific inquiry.

It would be valuable for the investigators to clarify this statement in the revised proposal; it is not clear which patients will be included in the analysis: "A given data from one patient either can be fit to one of the equations with a p value of less than 0.1 or it cannot. If it cannot then it is not included in the analysis."

I am not convinced that the analysis the authors propose will be clinically robust when tested in practice. But I am giving an approval because I think this is a valid use of the data.

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 #: 2017-2036   )

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?	Unsure, further clarification from requestor is needed
3. Can the proposed research be reasonably addressed using the requested data?	Unsure, further clarification from requestor is needed
4. Recommendation for this data request:	Not Approve

Comments:

1. Can the team provide additional details on how growth and regression are determined? Is it based on imaging? What modality?

2. It looks like the key endpoint for this study is estimating growth and regression rates and fractional cell kill but it is not clear how growth and regression rates will be ascertained from the data sets as these are not endpoints in either clinical study. The available tumor measurements only take account of a selection of lesions, not at all representative of the overall increase or decrease in tumor burden. Is the growth rate derived from PSA doubling time?

3. This is an interesting proposal to estimate tumor regression and growth rates, along with fractional cell kill and overall survival, among men with prostate cancer treated with abiraterone acetate in 2 clinical trials. While I think I understand the purpose of the analysis, it could have been written a bit more clearly. I would have preferred to see more explicit text describing how tumor regression and growth rates, along with fractional cells killed, would be estimated. The citations were not embedded in the article, so I presume the method is similar to the mathematical model described in citation 7 (Lancet Oncol. 2017; 18:143-154), but I was not certain.

4. In addition, I was confused by aim 2 - the application of these estimates to other data sources. This aspect of the proposal is not well described (no methods or statistical analysis plan is focused on the application of the estimates to other public data sources or the VA data). The work to calculate the growth rate estimates and correlate to observed survival from the shared abiraterone acetate clinical trial data is clearly described. I would advise focusing this proposal on that aspect of aim 2.

5. In addition, specific information about the mathematical model would be useful to provide. For instance, what % of missing data can be tolerated before a patient needs to be excluded from analysis (1%, 10%?); the first sentence of the statistical analysis plan was difficult to comprehend; can the time point for landmark analysis be pre-specified (the text says only that it will be pre-specified - but the purpose of the proposal is to pre-specify the methods).

Principal Investigator

First Name: Antonio
Last Name: Fojo
Degree: MD, PhD
Primary Affiliation: Columbia University Medical Center/ James J. Peters VA Medical Center
E-mail: atf2116@cumc.columbia.edu
Phone number: 718-584-9000 ext 3874
Address: 130 W. Kingsbridge Rd Suite 3H

City: Bronx
State or Province: NY
Zip or Postal Code: 10468
Country: USA
SCOPUS ID: 35392053300

General Information

Key Personnel (in addition to PI):

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

Conflict of Interest

http://yoda.yale.edu/system/files/coi_fojo2.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
Associated Trial(s):

1. 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
2. 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

Determine the growth and regression rate constant and the fractional cell kill of abiraterone acetate in prostate cancer

Narrative Summary:

Prostate Cancer is the most common cancer in men, monitored by PSA, a serum marker accurately reflecting disease burden. Treatment efficacy is the net result of two simultaneous phenomena: regression of the sensitive tumor fraction and the growth of the resistant tumor fraction increasing at a fixed rate. Using a novel method of analysis we can discern these two simultaneous processes and establish for each tumor its rate of growth and regression during treatment. In this proposal we will determine efficacy of abiraterone by establishing correlations between the rate of growth and the overall survival, the FDA gold standard for efficacy.

Scientific Abstract:

Background. When an oncologist treats a patient with cancer the fraction of cancer sensitive to the therapy regresses while simultaneously the fraction resistant to therapy grows, both at a constant rate. The quantity of tumor may be larger or smaller than at the start, depending on which of the two simultaneous phenomena dominates. Using a novel yet extensively tested method of analysis we can discern these two simultaneous processes and establish for each tumor its rate of growth and regression during treatment. Treatment efficacy is the net result of two simultaneous phenomena, correlate exceptionally well with overall survival - the FDA gold standard for efficacy.

Objective: Examine outcomes in patients with prostate cancer treated with abiraterone.

Study Design. Retrospective analysis of NCT00638690 and NCT00887198 data.

Participants. Patients with prostate cancer.

Main Outcome Measure(s). The mean and medians of growth rate constant, regression rate constant and fractional cell kill are estimated and these are in turn utilized for statistical analysis.

Statistical Analysis.
Comparisons of growth rate distribution: Wilcoxon two-sided/ Kruskal Wallis tests.
OS probabilities: Kaplan-Meier method.
Landmark survival analysis of OS: landmark and Cox model.

Brief Project Background and Statement of Project Significance:

Background. Prostate cancer (PC) is the second most frequently diagnosed cancer in men and second leading cause of cancer death in males in the United States and Europe. For patients with locally advanced PC or those who develop metastatic disease, medical androgen deprivation therapy (ADT) or surgical castration has been the mainstay of treatment given the importance of the androgen receptor (AR) in the development and progression of PC. However, despite the ability of ADT to induce biochemical and clinical response in >90% of treated patients, progression to castration-resistant prostate cancer (CRPC), defined as progressive disease despite low testosterone levels, occurs after a median of 24–36 months. And while we generally think of PC as an indolent disease, median survival times of patients with metastatic CRPC (mCRPC) are only 9.1 to 21.7 months without treatment. SEER data show an estimated 220,800 new cases and 27,540 deaths due to PC in 2015. Death occurs despite improved systemic therapies for PC.
The recognition that CRPC retained androgen responsiveness and that interfering with androgen signaling could bring about tumor responses in CRPC has fueled a revolution in treatment – with an emphasis on the development of therapies aimed at targeting the AR. The approval of abiraterone and then of enzalutamide provided novel, tolerable and effective options to target the AR. Additionally in the past two years, three RCTs evaluated the early addition of docetaxel to ADT in "hormone-sensitive metastatic prostate cancer" and the results have been both surprising and gratifying. So that a recent meta-analysis concluded the data "clearly shows a significant impact on OS with the concomitant administration of docetaxel and ADT in patients with metastatic hormone-sensitive prostate cancer".
Project Significance. The increasing numbers of options for PC present therapeutic challenges. Because none is curative, tolerability and efficacy influence decisions. Our approach allows one to estimate and update a tumor's growth rate with each PSA result. This growth rate can be compared against values in other patients receiving the

same or different therapies including those enrolled in pivotal clinical trials; or Veterans that have received the same therapy or even a subset – for example, African American men older than 70 years of age. It allows one to make optimal choices by leveraging "big data" to inform decisions on individual patients.

We have explored tumor burden in mCRPC using data from several studies including single and multi-institutional data sets. We have explored tumor burden in mCRPC using data from several studies including single and multi-institutional data sets. We are now poised to explore additional patient data, including data hosted on YODA. This data will allow us to benchmark the efficacy of abiraterone in Veterans using data from the VHA records and in turn, allow us to compare the efficacy of both abiraterone and enzalutamide in this very diverse patient population.

Specific Aims of the Project:

AIM 1: Harvest data and estimate the growth and regression rates and the fractional cell kill of prostate cancer treated with abiraterone acetate.
Aim 1.1 Harvest data from patients enrolled in NCT00638690 and NCT00887198 to estimate the growth and regression rates as well as the fractional cell kill while receiving therapy.
AIM 2: Assess the efficacy of abiraterone acetate as a prostate cancer therapy by establishing correlations between the rate of growth and the overall survival.
Aim 2.1: Conduct statistical comparisons of the abiraterone acetate data to data previously evaluated by the investigators from (1) other publicly available databases and (2) Veterans treated within the Veterans Health Administration system.

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 populationsPreliminary research to be used as part of a grant proposal

Research Methods

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

We developed an R package, designated tumgr, 9 that allowed us to obtain tumor growth rates. In cases where all parameters were significant predictors of tumor quantity (quantity at time t /quantity at time 0, given the specified cut-off value of 0.10) in more than one model, the model that minimizes the Akaike Information Criterion (AIC) will be selected. The selected model will minimize AIC with AIC=[(-2·log likelihood of model) + (2·# parameters in model)]. Patient data sets with insufficient, numerically erroneous, or missing data will not be analyzed and will be noted as excluded with one of the following explanations: no PSA data, only 1 PSA evaluation, or error data. The analysis aims to include all analyzable data. Experience with nearly 20,000 individual patient data has shown that, on average, 90-95% of data in a clinical trial can be fit to the formula used in this analysis. Only data that cannot be described by one of the basic equations is not analyzed.

Main Outcome Measure and how it will be categorized/defined for your study:

• Growth rate constant
• Regression rate constant
• Fractional cell kill

These values are assigned both numerical and logarithmic numbers. For entire data sets, mean and medians with confidence intervals are estimated and these are in turn utilized for statistical analysis.

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

Growth rate constant, regression rate constant and fractional cell kill will be estimated for individual patients and for specific subgroups. In each subgroup, mean and medians with their confidence intervals will be used to assess statistical similarities or not. As the values represent a continuum and not predefined bins, there is no categorization. The only categorization is a descriptive one where each individual data set is defined according to whether one or more of three variables (growth rate constant, regression rate constant and fractional cell kill) comprise equation that best describes the fit of the data. All of these methodologies have been validated and are described in our previous publications.

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

your study:

Overall survival, progression free survival, age, racial/ethnic demographics, and if available Gleason scores.

Statistical Analysis Plan:

Patient datasets with sufficient data will be analyzed and noted using the novel formulae and in dictated as either included (with selected model indicated) or excluded (non-significant predictors where no model converged indicated as 'not fit' or those with only 2 data points differing by <20%). Comparisons of growth rate distributions will be done by Wilcoxon two-sided tests (where groups analyzed = 2) or by Kruskal Wallis tests (where groups analyzed >2) followed by a Dunn's test for pairwise difference if there is an overall difference. The Kaplan-Meier method will be used to estimate OS probabilities. Landmark survival analysis of OS will be performed using a landmark (in month) and a Cox regression will be performed with the log of g (estimated from data prior to landmark) as the single predictor using the R package survival to obtain a measure of concordance (C-index) between g and OS. Landmark number month will be chosen as a time point that will be far enough after the initiation of treatment to allow for reliable estimation of g, but close enough in time to randomization so that a limited number of patients have already died. This time point will be pre-specified and will be the only time point examined. Additionally, the incremental value of g was evaluated by comparing a Cox model containing baseline variables (age, race, treatment) with a model containing baseline variables and g, to obtain the change in the C-index after the addition of g information using 1000 iterations of perturbation re-sampling via the R package survC1. By incremental g evaluation we are looking to define how much additional model accuracy (as assessed by the C-index) the addition of g to the model added.

Finally, because the formulae used will include time (t), the analysis is not affected by assessment intervals such that if the intervals of two studies are different or if scheduling difficulties require some intervals to be longer or shorter the estimates of phi, g and d, are not affected since these estimates are a global average over all data points for that patient. This in turn allows the data to be presented as one output. Note also that estimates of phi are determined not only by the falling part of the tumor size curve (PSA as surrogate for this) but also by data form the re-growing phase.

Project Timeline:

0-2 months: Analyze data
2-4 months: Assess efficacy and compare results to other therapies
4-6 months : Submit for publication

Dissemination Plan:

Anticipated products: Manuscript within 6 months.
Target Audience: Medical Oncologists and Outcomes researchers
Expectation for study manuscript(s): highly statically valid comparison of data: novel data analysis in a very diverse group of patients.
Publications: High impact journal such as Lancet Oncology, JAMA and JAMA Oncology

Bibliography:

1. Stein WD, Figg WD, Dahut W, et al. Tumor growth rates derived from data for patients in a clinical trial correlate strongly with patient survival: a novel strategy for evaluation of clinical trial data. Oncologist 2008a; 13:1046–1054.
2. Stein WD, Yang J, Bates SE, Fojo T. Bevacizumab reduces the growth rate constants of renal carcinomas: a novel algorithm suggests early discontinuation of bevacizumab resulted in a lack of survival advantage. Oncologist 2008b; 13:1055–1062.
3. Stein WD, Huang H, Menefee M et al. Other paradigms: growth rate constants and tumor burden determined using computed tomography data correlate strongly with the overall survival of patients with renal cell carcinoma. Cancer J. 2009; 15:441-7.
4. Stein WD, Gulley JL, Schlom J et al. Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. Clin Cancer Res 2011; 17:907–917.
5. Stein WD, Wilkerson J, Kim ST, et al. Analyzing the pivotal trial that compared sunitinib and IFN-alpha in renal cell carcinoma, using a method that assesses tumor regression and growth. Clin Cancer Res 2012; 18:2374–2381.

6. Wilkerson J. tumgr: Tumor Growth Rate Analysis. R package version 0.0.4. 2016. http://CRAN.R-project.org/package=tumgr (accessed Mar 25, 2016).

7. Wilkerson J, Abdallah K, Hugh-Jones C, Curt G, Rothenberg M, Simantov R, Murphy M, Morrell J, Beetsch J, Sargent DJ, Scher HI, Lebowitz P, Simon R, Stein WD, Bates SE, Fojo T. Estimation of tumour regression and growth rates during treatment in patients with advanced prostate cancer: a retrospective analysis. Lancet Oncol. 2017; 18:143-154.