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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 and second leading cause of cancer death in males in the US and Europe. For patients with locally advanced PC or those who develop metastatic disease, androgen deprivation therapy (ADT) or surgical castration has been the mainstay of treatment given the importance of the androgen receptor (AR) in development and progression of PC. However, despite induction of biochemical and clinical response by ADT in >90% of treated patients, progression to castration-resistant prostate cancer (CRPC), defined as progression despite low testosterone levels, occurs after a median of 24–36 months. And while we generally think PC is an indolent disease, median survival times of patients with metastatic CRPC (mCRPC) are only 9.1- 21.7 months without treatment.
The recognition that CRPC retained androgen responsiveness and that interfering with androgen signaling could effect tumor responses in CRPC has fueled a revolution in treatment –emphasizing the 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.
No elements other than PSA values and the dates when they were obtained are needed. The added value is that we are confident we will establish a correlation between the growth rate constant and overall survival the FDA "gold standard". This then emerges as a very valuable finding as regards clinical trials and also the administration of this drug class in patients.

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.

Note: The efficacy of abiraterone is already established. It is approved by the FDA. This will establish a correlation between the growth rate constant on abiraterone and overall survival (OS), an important finding given the well-established value of OS as the FDA "gold standard". That we will establish this we have no doubt. So what we will do is estimate the growth rate constants in all of these patients and this will be a measure in that patient of a value that correlates with OS and this of course is a measure of efficacy

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, AVAILABLE at R-Studio that estimates tumor growth and regression rates. Four equations are evaluated and the one that minimizes the Akaike Information Criterion (AIC) is selected as the best fit. Experience with nearly 20,000 individual patient data has shown that, on average, 90-95% of data in a trial can be fit to the equations. Only data not described by one of the four equations is not analyzed. We will focus on the rate of growth, but also examine and understand the meaning / value of simultaneously occurring regression rate.
Growth rates can be estimated from PSA data or tumor measurements; we have used both. We recognize available tumor measurements are of only some lesions. We do not calculate "PSA doubling times" since they cannot be estimated when tumor quantity is shrinking and then growing as occurs with abiraterone, but only after the nadir is reached and "clinically" only growth is occurring; our equations include both a regression and growth rate constants.;We have conducted and published analyses using imaging measurements, PSA values, calcitonin values (in medullary thyroid cancer), and M spikes (in multiple myeloma).

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 using four formulae and indicated 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 estimate OS probabilities. Landmark survival analysis of OS 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 will be chosen as a time point far enough after treatment initiation to allow for reliable estimation of g, but close enough to randomization so that a limited number of patients have died. Additionally, the incremental value of g will be 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.
As we note above, "Patient datasets with sufficient data will be analyzed and noted using four formulae and indicated as either included (with selected model indicated) or excluded (non-significant predictors where no model ..... by <20%)". 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. With prostate cancer about 88-92% of data can be fit. Data that does "not fit" is often patients with very low numbers that "just bounce around" or those with only two values who then went off study. As for landmark analysis we can argue that since there is no established standard and quite frankly having done many of these, they add very little to an analysis. So basically we do as we did in our Lancet Oncology manuscript, we conduct multiple landmark analyses to satisfy everyone. No one can say for such a trial what MUST be the landmark analysis. So any value given is pulled out of the air. Basically as I said we do multiple landmark analyses and all corroborate each other.
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.
The first step will be to estimate the rates of growth and regression in the YODA data. If OS data is available we are CONFIDENT we will establish a correlation with OS. With that data in hand we can then use it as a "benchmark or reference" with any other data set. We have data on over 5000 VA patients treated with abiraterone and enzalutamide including the largest number of African American men ever studied. That data has been analyzed and it is validated, incredibly robust, correlates with OS, and has been analyzed across the entire VA system. With the YODA analysis finished we are literally then "just a few clicks away" from comparing the data in the YODA data set to our own data. We have done these comparisons extensively.

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:

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

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