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General Information

Key Personnel (in addition to PI): **First Name:** Zachary
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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): 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

Predictors of Survival in a Trial of Abiraterone Acetate for Men with Metastatic Castration-Resistant Prostate Cancer and No Prior Chemotherapy

Narrative Summary:
In a previous phase 3 trial of chemo-naive men with mCRCP randomized to abiraterone acetate + prednisone vs prednisone, men in the abiraterone group had a distinct survival advantage. At a median follow-up of 49.2 months, there were 741 mortalities (68% of sample). The objective of this study is to perform a post hoc analysis to determine predictors of survival. Specific predictor variables will include demographic, clinicopathologic and secondary/additional treatment. Identifying 'very high risk' men for death in an already 'at-risk' population will allow delineation of patients that should be considered for additional clinical trials, further treatment, and/or hospice care, etc.

Scientific Abstract:
Background: Abiraterone acetate is an androgen biosynthesis inhibitor treatment option for men with metastatic castration-resistant prostate cancer (mCRPC). A previous phase III, randomized, controlled, double-blind study compared prednisone + abiraterone or prednisone + placebo, demonstrating an overall survival (OS) benefit for those receiving abiraterone.
Objective: To identify post-hoc predictors of OS, including subsequent treatment modalities, in men previously randomized to prednisone + abiraterone or prednisone + placebo.
Study Design: Post-hoc analysis of data from a phase III, randomized, controlled, double blind study.
Participants: 1088 men with mCRPC randomized to receive prednisone + abiraterone or prednisone + placebo.
Main Outcome(s): (i) Identify demographic, socioeconomic and clinicopathologic predictors of OS; (ii) Identify predictors of early mortality (?1 year from randomization) among men with mCRPC; (iii) Identify the most impactful combination of abiraterone (or placebo for the control arm) and subsequent treatment on OS.
Statistical Analysis: Descriptive statistics will be used to compare predictor variables between groups. Multivariable Cox Proportional hazards modelling will be used to generate hazards ratios for predictors of overall survival. The Kaplan-Meier method using the log-rank test will be used to assess median OS, stratified by groups where appropriate. Multivariable logistic regression modelling will be used to generate odds ratios for identifying predictors of early mortality (?1 year from randomization).

Brief Project Background and Statement of Project Significance:
Prostate cancer (PCa) is the most commonly diagnosed solid organ malignancy in the United States and remains the second leading cause of cancer deaths among men [1]. Most advanced PCa responds initially to androgen deprivation therapy (ADT), although patients ultimately progress despite castration on average between 1-3 years after starting ADT. Prior to 2004, once patients progressed on ADT, treatment was ultimately palliative. Since then, seminal articles demonstrated that docetaxel chemotherapy improves survival in men with metastatic castration-resistant prostate cancer (mCRPC) [2,3]. Subsequently, other agents (abiraterone, enzalutamide, sipuleucel-T and cabazitaxel) have been approved by the FDA in the mCRPC setting.
Abiraterone acetate is an androgen biosynthesis inhibitor that demonstrated increased survival in men with mCRPC who previously failed chemotherapy [4]. In this landmark trial, 1195 patients were randomly assigned (2:1) to receive prednisone + abiraterone vs prednisone + placebo. After 12.8 months of follow-up, patients receiving abiraterone had a significantly longer overall survival (OS) compared to the placebo group (14.8 vs 10.9 months; HR 0.65, 95%CI 0.54-0.77). A subsequent trial two years later randomizing 1088 chemo-naïve patients to either prednisone + abiraterone or prednisone + placebo also demonstrated an OS survival for patients receiving abiraterone (median not reached vs 27.2 months for prednisone alone; HR 0.75, 95%CI 0.61-0.93) [5]. A final analysis of abiraterone in chemo-naïve patients was recently published [6]. At a median follow-up of 49.2 months, 773 of 1088 men in the study had died, with a significantly improved OS in men receiving abiraterone compared to placebo (34.7 vs 30.3 months; HR 0.81, 95%CI 0.70-0.93).
In their final analysis, Ryan et al. [6] demonstrate a statistically and clinically significant improvement in OS for abiraterone at 4 years follow-up. As part of the supplementary tables of this manuscript, Ryan et al provide an exploratory multivariable analysis (MV) of OS. In this model, significant predictors of OS include abiraterone, age, and baseline PSA, LDH, alkaline phosphatase, hemoglobin, and bone metastasis. There are a number of important factors that may contribute to OS that were not assessed in this exploratory MV analysis [6] that we will assess in the proposed study: (i) the impact of demographics and socioeconomic factors (ie. Race, marital status, geographical location, etc); (ii) predictors of early (?1 year) mortality; (iii) the impact of secondary therapies on OS, specifically the sequence of secondary therapies. In the experimental arm (abiraterone), 67% of patients had subsequent therapy and 80% of patients in the control arm (placebo) received secondary therapy. Very little is known regarding the appropriate sequence of therapy in the armamentarium of treating mCRPC and the impact on OS. This dataset provides an excellent opportunity to gain knowledge regarding additional factors that may

contribute to OS and provide further granularity to the impact of subsequent therapies on OS in patients with mCRCP.

Specific Aims of the Project:
Aim #1: Assess the impact of additional variables on OS.
Objective #1: To incorporate additional demographic, socioeconomic and clinicopathologic variables into multivariable Cox proportional hazards models in order to identify predictors of OS.
Hypothesis #1: Non-white, unmarried and men with poor socioeconomic status will be at a survival disadvantage.

Aim #2: Assess predictors of early mortality (randomization to ?1 year).
Objective #2: To identify predictors of early mortality (?1 year) compared to patients that died >1 year after randomization or were alive at censoring.
Hypothesis #2: Patients with significant comorbidities and/or large metastatic burden of disease and/or rapid disease progression will be at risk for early (?1 year) mortality.

Aim #3: (a) Assess the impact of subsequent therapy after abiraterone (or placebo for the control arm) on OS, and (b) sequence of subsequent therapy on OS.
Objective #3: To identify post-abiraterone therap(ies) that improve OS and attempt to delineate appropriate secondary therapy sequence for improving OS.
Hypothesis #3: Men receiving chemotherapy post-abiraterone will confer a survival advantage compared to those receiving other secondary therapies.

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: 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”

Inclusion criteria (men in the above dataset):
• >18 years of age
• Complete survival data including time from randomization to death/censoring
• Complete secondary therapy data

Exclusion criteria:
Patients lost to follow-up

Main Outcome Measure and how it will be categorized/defined for your study:
The main outcome variable in this study will be overall survival, which will be categorized as a binary variable yes/no. Time from randomization to death in months will also be recorded.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The main predictor variable in this study will be modality of secondary/subsequent therapy. This will be defined as: none, abiraterone acetate, cabazitaxel, docetaxel, enzalutamide, ketoconazole, radium-223, spiuleucel-T.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Other variables of interest in the study:
• Age (year, continuous)
• Race (white vs black vs other)
• Marital status (married vs unmarried vs unknown)
• Gleason score at initial diagnosis (?7 vs ?8 vs unknown)
• PSA at initial diagnosis (ng/mL, continuous)
• Baseline PSA at randomization (ng/mL, continuous)

• PSA doubling time (?10 vs >10 months)
• Primary treatment (surgery vs radiation vs other vs hormonal vs none)
• Extent of disease (bone only vs soft tissue or node vs both)
• Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1)
• Charlson Comorbidity Index (CCI) (0-2 vs >2) [7]
• Brief Pain Inventory-Short Form score (0-1 vs 2-3 vs ?4)
• Region (North America vs Other)
• LDH (U/L continuous)
• ALK-P (IU/L, continuous)
• Baseline hemoglobin (dg/L, continuous)
• Time to opiate use (months, continuous)
• Time to deterioration in ECOG performance status ?1 point (months, continuous)
• Time to PSA progression (months, continuous)
• Time to pain progression (months, continuous)
• RECIST response (complete vs partial vs stable vs progressive)

Statistical Analysis Plan:
Aim #1: Assess the impact of additional variables on OS.
Statistical Plan #1: Use descriptive statistics to compare patient variables (see Main Predictor & Other Variables of Interest) of those that were alive at the study conclusion to those that died. Subsequently, significant predictor variables and clinically relevant variables will then be incorporated into a multivariable Cox Proportional hazards model in order to identify predictors of OS. Median OS will then be determined using the Kaplan-Meier method using the log-rank test.

Aim #2: Assess predictors of early mortality (randomization to ?1 year).
Statistical Plan #2: Use descriptive statistics to compare patient variables (see Main Predictor & Other Variables of Interest) of those that died ?1 year after randomization to patients that died >1 year after randomization or were alive at censoring. Subsequently, significant predictor variables and clinically relevant variables will then be incorporated into a multivariable logistic regression model in order to identify adjusted predictors (odds ratio) of mortality ?1 year (compared to >1 year/alive at censoring).

Aim #3: Assess the impact of subsequent therapy after abiraterone (or placebo for the control arm) on OS, and sequence of subsequent therapy on OS.
Statistical Plan #3: Use descriptive statistics to compare patient variables (see Other Variables of Interest) among groups of patients that received secondary therapy after abiraterone or placebo (see Main Predictor variable for combinations of abiraterone + subsequent treatments). Subsequently, compare treatment combinations in a multivariable Cox Proportional hazards model (adjusting for significant predictor variables and clinically relevant variables, as well as using time-varying covariates to adjust for death prior to subsequent treatment and to account for immortal time bias) in order to identify the most impactful and significant treatment combinations on OS. Median OS, stratified by treatment combination, will then be determined using the Kaplan Meier method using the log-rank test.

Project Timeline:
Anticipated project start date: within 1 month of receiving access to data (ie. February 1, 2017)
Analysis completion date: April 1, 2017
Date manuscript drafted: June 1, 2017
Manuscript first submitted for publication: August 1, 2017
Date results reported back to YODA Project: August 1, 2017

Dissemination Plan:
This study is projected to generate an abstract for conference presentation and a high-level peer reviewed manuscript.
Anticipated conferences for presentation:
• American Society of Clinical Oncology
• European Association of Urology
• American Urological Association
• Canadian Urological Association
• Society of Urologic Oncology

Peer-Reviewed Journal Submission Plan:
• Journal of Clinical Oncology
• If rejected, then European Urology
• If rejected, then Cancer
• If rejected, then Journal of Urology
• If rejected, then Urologic Oncology
• If rejected, then BJU International
• If rejected, then Prostate Cancer and Prostatic Diseases
• If rejected, then Urology
• If rejected, then Clinical Genitourinary Cancer

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4. de Bono JS, Logothetis CL, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995-2005.
5. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previoius chemotherapy. N Engl J Med 2013;368(2):138-148.
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7. Charlson ME, Pompei P, Ales KL, MacKensize CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.