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General Information

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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

Conflict of Interest

https://yoda.yale.edu/system/files/abdollah-coi_0.pdf
https://yoda.yale.edu/system/files/keeley-coi_0.pdf
https://yoda.yale.edu/system/files/modonutti-coi_0.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. 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
2. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-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

Testing The Impact Of Enzalutamide And Abiraterone On Overall Survival In Patients With Metastatic Castration-Resistant Prostate Cancer

Narrative Summary:

Several treatments for metastatic castration-resistant prostate cancer (mCRPC) patients have been developed during the last years, including enzalutamide and abiraterone acetate (AA). Currently, prognostic models predicting oncological outcomes of mCRPC patients receiving AA or enzalutamide are lacking. We previously developed a nomogram predicting the overall survival of mCRPC patients undergoing first-line chemotherapy with docetaxel. We are now planning to investigate how our model performs on patients receiving enzalutamide or AA. Moreover, we want to study if patients receiving docetaxel, AA, or enzalutamide share the same prognostic predictors.

Scientific Abstract:

Background:
Nomograms predicting the overall survival (OS) of metastatic castration-resistant prostate cancer (mCRPC) patients are lacking.

Objective:
We previously developed a multi-trial based model predicting the OS of mCRPC patients undergoing docetaxel. Now we aim to investigate how our model performs on patients receiving enzalutamide or AA. Moreover, we want to study if patients receiving docetaxel, AA, or enzalutamide share the same prognostic predictors.

Study design:
We'll test the performance of the novel prognostic model in two therapeutic settings using patient-level data from three RCTs.

Participants:
We will use data from the COU-AA-302 trial (NCT00887198) and from a prospective observational registry of mCRPC patients (NCT02236637), as well as from the PREVAIL trial (NCT01212991).

Main Outcome Measure(s):
The OS of mCRPC patients treated with enzalutamide or AA.

Statistical Analysis:
1. We will investigate if the predictors of OS of patients treated with docetaxel are still significant in patients undergoing enzalutamide or AA.
2. If the performance of our model is suboptimal for patients treated with enzalutamide or AA, we will adjust the coefficients of the model to get a better fit.
3. We will test the discrimination of the model using the time-dependent area under the curve.

4. We will use Kaplan-Meier survival curves to describe the OS of patients receiving enzalutamide or AA.
5. We will calibrate the model using calibration curves.

Brief Project Background and Statement of Project Significance:

Due to its frequency in the population, prostate cancer is a global challenge far from being solved. 1 Metastatic castration-resistant prostate cancer (mCRPC) represents the most advanced stage of the disease, with these patients having an unfavorable prognosis. 2–4 Several treatments have been developed during the last decade, including two new drugs, enzalutamide and abiraterone acetate. 5–8 However, head to head comparisons in efficacy between these new compounds are lacking. In this setting, the development of reliable prognostic models would permit the stratification of patients into risk classes yielding a more accurate risk-benefit assessment of the current therapies. Moreover, prognostic models are of critical importance in the study design of clinical trials. To assess this issue, we already developed a multi-trial based nomogram predicting overall survival of metastatic castration-resistant prostate cancer patients receiving docetaxel-based chemotherapy or supportive/palliative care. To develop this prognostic model, we used data of the control arm of five randomized clinical trials: ASCENT 2, CELGENE/MAINSAIL, VENICE, and ENTHUSE 33. 9–12

Specific Aims of the Project:

We are going to investigate how our novel nomogram predicting overall survival of mCRPC patients undergoing docetaxel performs on patients receiving abiraterone acetate or enzalutamide. Moreover, we want to study if the predictors of overall survival that we found for patients undergoing docetaxel are common to patients receiving abiraterone acetate or enzalutamide.

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:
We are going to use patients level data from the requested databases (NCT00887198 and NCT02236637) as well as data from the PREVAIL trial (NCT01212991; data request submitted on Vivli).

Inclusion Criteria:
1. ?18 years.
2. Life expectancy >3 months.
3. Histopathologically or cytologically proven adenocarcinoma of the prostate
4. Metastatic disease.
5. Maintaining castrate status.
6. Progressive disease while receiving hormonal therapy or after surgical castration.
7. Adequate hematologic, cardiac, renal, and hepatic function.
8. Eastern Cooperative Oncology Group ? 2.

Exclusion Criteria:
1. Prior cytotoxic chemotherapy.
2. Prior isotope therapy.
3. Prior malignancy (adequately treated basal cell or squamous cell skin cancer are allowed).
4. History of symptomatic central nervous system or brain metastases.
5. Must not have had significant active cardiac disease within the previous six months.
6. A history of clinically significant medical, surgical, or psychiatric disease that would place the subject at an unacceptable risk for study entry.
7. Participation in another clinical trial and any concurrent treatment with any investigational drug.

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

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The outcome of interest is the difference in overall survival between patients receiving docetaxel, enzalutamide, or abiraterone acetate.

Overall survival is defined as the time from randomization to time of death or last available follow-up.

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

In the first place, we are going to use the variables that were significant as independent predictors of overall survival (OS) at the univariable analysis of our previous model:
1. age
2. body mass index (BMI)
3. ECOG performance status
4. prostate specific antigen (PSA)
5. sites of metastasis
6. platelets
7. hemoglobin
8. neutrophils
9. aspartate transaminase (AST)
10. alkaline phosphatase (ALP)
11. calcium
Secondly, this study aims to check for new independent predictors of OS in patients receiving abiraterone acetate or enzalutamide.

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

None.

Statistical Analysis Plan:

Recently we developed a nomogram predicting overall survival (OS) of patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing docetaxel. Patients enrolled in the control arm of five randomized clinical trials (ASCENT 2, VENICE, CELGENE/MAINSAIL, ENTHUSE 14, ENTHUSE 33) were randomly split into a training (70%) and validation cohort (30%). In the training cohort, Cox regression tested the prognostic significance of all available variables as a predictor of OS. Independent predictors of OS on multivariable analysis were used to construct a novel multivariable model (nomogram). The accuracy of this model was tested in the validation cohort using the time-dependent area under the curve (tAUC), and calibration curves. Currently, the results of this study are under peer review on the Journal of Urology.

In regards to the upcoming project, using the just described prognostic model, we are going to:
1. establish if the predictors of OS that we found for patients treated with docetaxel are still significant in patients undergoing enzalutamide or abiraterone acetate.
2. if the performance of our nomogram is suboptimal for patients treated with enzalutamide or abiraterone acetate, we will adjust the coefficients of the model to get a better fit.
3. test the discrimination of the model using the tAUC.
4. use Kaplan-Meier curves to describe the OS in the different populations, after stratifying patients into low- vs. high-risk groups based on the median predicted value of our novel nomogram.
5. calibrate the model using calibration curves.
Software Used:
RStudio
Project Timeline:

• Project start date: October/November 2020. The data analysis will start as soon as we receive the data.
• Analysis completion date: November/December 2020.
• Date manuscript drafted and first submitted for publication: February 2021.
• Date results reported back to the YODA Project: March 2021.

Dissemination Plan:

We are planning to publish our data on a specialized journal such as the Journal of Clinical Oncology (JCO).

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/prognostic_model.pdf