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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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/02/YodaCOI.pdf
https://yoda.yale.edu/wp-content/uploads/2019/11/coi_yoda_yang.pdf
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https://yoda.yale.edu/wp-content/uploads/2021/12/COI-form-HK.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. NCT02257736 - 56021927PCR3001 - A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

External Validation of a Prognostic Model of Overall Survival In Men with Metastatic Castration-Resistant Prostate Cance

Narrative Summary:

Background: We have previously developed and externally validated a prognostic model of overall survival (OS) in men with mCRPC treated with docetaxel (D), which included eight predictors: opioid analgesic use, ECOG performance status, albumin, disease site, LDH, hemoglobin, PSA, and alkaline phosphatase. We have used this model to develop prognostic risk groups. We seek to externally validate this model in a broader group of men with mCRPC and in specific subgroups (White, Black, Asian patients, different age groups) and to validate the two and three prognostic risk groups in this large dataset .

Scientific Abstract:

We have previously developed and externally validated a prognostic model of overall survival (OS) in

men with mCRPC treated with docetaxel (D), which included eight predictors [1]. This model was developed in patients treated with D and we would like generalize this model to contemporary patients in the era of potent AR inhibition with agents such as enzalutamide (ENZA) , abiraterone acetate (AA) and apalutamide (APA).
Objective; We seek to externally validate this prognostic model in a broader group of men with mCRPC and in specific subgroups (racial and ethnic group and different age groups) and to validate the two and three prognostic risk groups in this large dataset.
Study Design: This is a pooled analyses that will utilizine data from over 8000 mCRPC men randomized on 7 phase III trials to validate the prognostic model of OS: docetaxel (D) +/- zibotentan (ENTHUSE), D +/- lenalidomide (MAINSAIL), D +/- dasatinib (READY), D+/- custirsen (SYNERGY), tasquinimod trial (T/placebo), ENZA+/-AAP (A031201) and ACIS (AAP +/- APA) .
Participants: Men with mCRPC.
Main Outcome Measure(s); is OS and will be defined as the time from date of random assignment to date of death of any cause or last follow-up.
Statistical Analysis: We will evaluate the predictive ability of the prognostic model based on discrimination and calibration. We will first apply the estimated parameters from the prognostic model to each of the seven validation datasets and compute a risk score for every patient. The predictive performance of the model will be evaluated by computing the time-dependent area under the receiver operating characteristic curve (tAUC) for each of the validation sets. In addition, we will evaluate the performance of the prognostic model in subgroup of patients, in patients treated on the standard arm alone, in Asian, Black, and white patients and by age groups. Furthermore, we will calculate the 95% CI for each tAUC using the bootstrap approach. The prognostic model will be assessed for its calibration. In addition, we will validate the prognostic risk groups by comparing the survival distributions between the high-risk and low-risk groups, or the high-risk, intermediate-risk, or the low-risk groups. The Kaplan-Meier approach will be used to estimate the OS distribution in every dataset and the log-rank statistic will be used separately in the seven datasets to test if the survival distributions differed by the two or three prognostic risk groups.

Brief Project Background and Statement of Project Significance:

Prostate cancer is heterogeneous in all stages of disease both in terms of clinical behavior and morphology, with development and progression dependent upon androgens and androgen receptor (AR) activity. The tumor is initially androgen dependent but eventually it progresses to become androgen independent . Current front-line therapies for men with metastatic, castration-resistant prostate cancer (mCRPC) are androgen receptor targeted therapy, chemotherapy, and bone targeting agents [2-9].
The difficulty in treating men with mCRPC lies not only in heterogeneity of the disease (tumor specific factors), but also in the spectrum of patients who have the disease (host-specific factors). Thus, the variability in the expected outcome may be due to prognostic factors rather than in differences in treatments.
We have previously developed a prognostic model that predicts overall survival probability in men with metastatic castration-resistant prostate cancer (mCRPC) who were treated with first line docetaxel chemotherapy. The model was externally validated using the Enthuse-33 trial in patients treated with docetaxel and prednisone. The model has been used as a stratification factor in an ongoing phase II (NCT02218606) and a completed phase III mCRPC trials (NCT01949337). Currently, the prognostic risk score is used in selecting patients and to balance the prognostic factors between the treatment arms at randomization. This prognostic model was developed in patients with docetaxel and we would like generalize this model to contemporary patients in the era of potent AR inhibition with agents such as enzalutamide , abiraterone acetate and apalutamide. In addition, the performance of this model was not evaluated in diverse population

Specific Aims of the Project:

We seek to validate the risk score generated by the prognostic model by using external datasets in patients treated with docetaxel and in patients who were treated on tasquinimod, and in patients treated with AR inhibition (abiraterone acetate or enzalutamide, apalutamide) and to validate the two and three prognostic risk groups. Thus, the primary objectives of this analysis is to externally validate the prognostic model of OS in a broader group of men with mCRPC. In addition, we plan to

explore the predictive accuracy of the model in specific racial and age subgroups and treatment received and to validate the two and three prognostic risk group that is created by the model.
We are investigating the impact of liver metastases on clinical outcomes (OS, rPFS, ORR and PSA decline). We are also aiming to characterize exceptional responders and extreme resistance.
For last two of these aims, we plan to combine the data with other trial datasets

Study Design:

Meta-analysis (analysis of multiple trials together)

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 from over 8000 mCRPC men randomized on 7 phase III trials will be utilized to validate the prognostic model of OS: D +/- zibotentan (ENTHUSE), D +/- lenalidomide (MAINSAIL), D +/- dasatinib (READY), D+/- custirsen (SYNERGY), tasquinimod/placebo phase 3 trial, enzalutamide+/- abiraterone trial from the Alliance trial (A031201trial) and the ACIS trial (abiraterone acetate +/- apalutamide) .
We have access to the data from the 6 other trials and will be uploaded to the YODA platform to combine it with the data from the ACIS trial. Data are available through DUA with the sponsors on these trials:
ENTHUSE-33 (NCT00617669), READY (NCT00744497), MAINSAIL (NCT00988208), SYNERGY (NCT01188187), TASQUINIMOD (NCT01234311) and A031201 (NCT01949337).

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary endpoint is overall survival (OS) and will be defined as the time from date of random assignment to date of death of any cause or last follow-up.
1. Date of Randomization (MM/DD/YYYY)
2. Survival Status (Alive, dead)
3. Date of Last Observation or Follow-up (MM/DD/YYYY)
4. Date of Death (MM/DD/YYYY) or time to death since random assignment

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

The main predictors are:
1. ECOG Performance Status: 0, 1, 2, 3+
2. Opioid analgesic use 1) Yes, 2) No
3. Measurable Disease: 1) Yes, 2) No
4. Site of metastases: 1) Lymph nodes, 2) Bone, 3) Lung, 4) Liver, 5) other visceral metastases
5. LDH (and ULN for LDH)
6. Hemoglobin
7. PSA
8. Alkaline phosphatase
9. Albumin

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

In addition, age, race and ethnicity will be needed to describe the population and to assess the performance of the model in these subgroups.
1. Age (years)
2.Race
White
Black or African American
Asian
American Indian or Alaska Native
Missing/Not reported
3. Ethnicity
Hispanic or Latino
Not Hispanic or Latino
Not Reported

Statistical Analysis Plan:

We will evaluate the predictive ability of the prognostic model based on discrimination and calibration. We will first apply the estimated parameters from the prognostic model to each of the seven validation datasets and compute a risk score for every patient. The predictive performance of the model will be evaluated by computing the time-dependent area under the receiver operating characteristic curve (tAUC) for each of the validation sets [10]. In addition, we will evaluate the performance of the prognostic model in subgroup of patients, in patients treated on the standard arm alone, in Asian, Black, and white patients and by age groups. Furthermore, we will calculate the 95% CI for each tAUC using the bootstrap approach.
The prognostic model will be assessed for its calibration graphically by plotting the predicted probability of death evaluated at 18-, 22- 24-, and 30- months versus the observed probability at the respective time-points. In addition, we will validate the prognostic risk groups by comparing the survival distributions between the high-risk and low-risk groups (for two-risk group), or the high-risk, intermediate-risk, or the low-risk groups (in case of the three-risk group). The Kaplan-Meier approach will be used to estimate the OS distribution in every dataset and the log-rank statistic will be used separately in the seven datasets to test if the survival distributions differed by the two or three risk groups.

Software Used:

RStudio

Project Timeline:

We plan to submit an abstract for ESMO in late April/May 2022. We have access to all the datasets except the ACIS trial. It is expected that it will take 6 months to complete the analysis. It is anticipated that a manuscript will be submitted by December 2022.
We are still assembling additional data and plan to complete the analysis by December 2025

Dissemination Plan:

The results of these analyses will be submitted as abstracts and will be presented at International meetings such as ESMO and the Prostate Cancer Foundation Scientific Retreat. The first abstract is planned for ESMO in April/May 2022. Manuscripts will be written and will be submitted for Publication in peer review journals, such as Journal of Clinical Oncology, and Journal of the National Cancer Institute. Abstracts and manuscripts will be sent to the sponsor for review.
An abstract is planned for ESMO in April/May 2024. Manuscripts will be written and will be submitted for Publication in peer review journals, such as Journal of Clinical Oncology, and Journal of the National Cancer Institute. Abstracts and manuscripts will be sent to the sponsor for review.

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