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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/2023/02/malone_coi.pdf
https://yoda.yale.edu/wp-content/uploads/2023/02/roy_coi.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. NCT01715285 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)
2. NCT02489318 - A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects With Metastatic Hormone-sensitive Prostate Cancer (mHSPC)
3. NCT01946204 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men With Non-Metastatic (M0) Castration-Resistant Prostate Cancer
4. NCT02257736 - 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)
5. 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
6. 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

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

Research Proposal

Project Title

Improving Outcome in Advanced Prostate Cancer: a Pooled Analysis of Randomized Controlled Trials

Narrative Summary:

There remains a lack of prognostic models that can predict risk of progression or death in patients with advanced prostate cancer (APC). Moreover, although baseline factors can predict outcome with certain accuracy, this accuracy tends to fade out with evolving disease course. Our study aims to address this issue by better characterizing the prognosis of these patients. In addition, our work will explore whether treatment response and overall outcome differs based on receipt of prior prostate directed local therapy and exposure to different commonly prescribed classes of concomitant medicines such as blood sugar lowering pills, blood pressure lowering pills, blood thinners, etc. The results of this work would help personalization of treatment in men with APC.

Scientific Abstract:

Background: Despite significant advancement in the management of advanced prostate cancer (APC), a well-validated prognostic index that can predict for overall survival (OS) and progression-free survival (PFS) for this patient population is still lacking.
Objectives: We propose a pooled analysis of 6 different randomized trials to validate a multivariable prognostic model for APC patients treated with ARPI. We will initially use the already built prognostic model and if the model fails to achieve satisfactory performance, we will train and validate a new prognostic model to predict OS and PFS. Secondarily we would determine the prognostic association of dynamic changes in patient reported quality of life (QoL) parameters or serological markers such as hemoglobin (Hb), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), albumin, prostate-specific antigen (PSA), and lactate dehydrogenase (LDH) with OS and PFS. Thereafter, we will perform a secondary analysis of TITAN to determine whether treatment effect from first line ARPI on PFS and OS varies depending on receipt of prior prostate directed local therapy (radical prostatectomy [RP] and/or radiation therapy [RT]) and type of prior local therapy (RP or RT relative to no prior local therapy). A similar analysis will be done based on a pooled analysis of 6 trials. A similar approach will be used for defining the effect modifying role of exposure to concomitant medications such as statin, metformin, aspirin, among others. The effect modification will be analysed at the multiplicative and additive scale, respectively.
Design: Retrospective secondary pooled analysis of TITAN and LATITUDE study
Participants: Patients treated in the control and study arm of LATITUDE and TITAN.
Primary Outcome: Overall survival will be defined as the time from randomization to death from any cause.
Secondary outcomes: Progression-free survival defined as the time from randomization to the occurrence of radiographic progression, clinical progression, PSA progression, or death from any cause.
Statistical Analysis:
The static risk prediction model built from LATITUDE trial, will be evaluated on the curated data from LATITUDE for OS and PFS. Model discrimination and calibration will be evaluated. The index of prediction accuracy will be used to compare the overall model performances. If this model fails to demonstrate satisfactory performance, a new model will be trained and validated. For modelling the association of dynamic changes in the serological biomarkers and patient reported QoL scores with

OS, cancer-specific mortality, and PFS, we will apply a joint modelling framework. To determine the effect modifying role of prior prostate-directed local therapy and its type on treatment effect from first line ARPI in mHSPC, we plan to focus specifically on the TITAN dataset. We will build multivariable Cox proportional hazard models separately for OS, radiographic progression-free survival, and cancer-specific mortality which will include an interaction term between receipt of prior local therapy with the randomized treatment regimen.

Brief Project Background and Statement of Project Significance:

TITAN is a phase III randomized controlled trial that established role of apalutamide as a first line treatment for patients with metastatic hormone sensitive prostate cancer (1,2). The study included de novo metastatic prostate cancer as well initially diagnosed M0 prostate cancer which recurred or progressed to mHSPC. Final subgroup analysis from the TITAN study shows consistency in benefit obtained from use of apalutamide in both the de novo and the recurrent or progressive group (1). However, it is unknown whether receipt of prior prostate directed local therapy (LT) (including radical prostatectomy [RP] and radiation therapy [RT]) or type of prior LT (RP vs. RT) or exposure to concomitant medications such as metformin, statin, or aspirin influenced response to subsequent lines of androgen receptor pathway inhibitors (ARPI) in TITAN study. While there are separate prognostic models that are used to predict outcome for men with advanced hormone sensitive and hormone resistant prostate cancer, there is no unified prognostic model that can predict outcome of men with advanced prostate cancer when treated with ARPI. We used data from LATITUDE, a phase III randomized controlled trial in which men with de novo mHSPC were randomly allocated to either ADT plus abiraterone plus prednisone or ADT with dual placebos (3). Patients with non-missing data (n=1,058) were randomly split in a 70:30 ratio to training (n=743) and testing (n=315) sets. Elastic net regression was used for variable selection. A multivariable Cox regression model for OS was then fitted using the selected variables. The 11 prognostic variables in the final model were performance status, number of skeletal metastases, Gleason score, presence of liver metastasis, worst pain score, albumin, lactate dehydrogenase, prostate-specific antigen, hemoglobin, and treatment regimen. The tAUC for predicting OS at 2- and 3-years was 0.74 (95% CI, 0.67-0.80) and 0.72 (95% CI, 0.65-0.77), respectively (4). However, this model lacked external validation and calibration.
COU-AA-302 and COU-AA-301 are the two landmark trials that established the role of ARPI in chemotherapy naive and chemotherapy pre-treated metastatic CRPC patients while ACIS failed to show an OS benefit with addition of an ARPI doublet (abiraterone plus apalutamide) in chemotherapy naive mCRPC (5-7). SPARTAN is another landmark clinical trial that established use of apalutamide in first line setting in men with non-metastatic CRPC (nmCRPC) (8, 9).

We propose a pooled analysis of all 6 randomized studies to train and validate the predictive accuracy of a prognostic model that we have built using LATITUDE dataset for predicting OS and progression-free survival (PFS) in advanced prostate cancer patients. We also plan to determine if receipt of prior LT and type of prior LT and exposure to concomitant medications such as metformin, statin, and aspirin plays an effect modifying role on response to ARPI in advanced prostate cancer patients.

Our proposed work is anticipated to characterize and predict clinically significant outcomes in men with advanced prostate cancer which can be used to optimize further systemic treatment and/or LT for this patient cohort in routine clinical practice. We believe that this work will be crucial to future clinical research to stratify patients into different prognostic groups which could potentially lead to avenues to determine the best treatment combination in these patients.

Specific Aims of the Project:

Aim 1: Validation of a multivariable prognostic model in advanced prostate cancer patients treated with ARPI - We propose a pooled analysis of 6 randomized controlled studies (LATITUDE, TITAN, SPARTAN, ACIS, COU-AA-302, COU-AA-301) to validate a prognostic nomogram for advanced prostate cancer patients treated with ARPI. We will initially use the already built prognostic model (4). If the model fails to achieve satisfactory performance, we will train and validate a new prognostic model to predict OS and PFS.
Aim 1.1: Exploring association of dynamic changes in quality of life and serological markers of

inflammation with survival - We propose a pooled analysis of these studies to determine the prognostic association of dynamic changes in QoL metrics and serological markers of inflammation such as hemoglobin, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, lymphocyte to monocyte ratio, and lactate dehydrogenase independently with OS and PFS.
Aim 2: Determining the effect modifying role of prior LT on response to ARPI - We will perform a pooled analysis of these 6 trials to determine if the effect of ARPI on PFS and OS varies depending on receipt of prior prostate directed LT and type of prior LT (radical prostatectomy or radiation therapy relative to no prior LT) after adjustment for confounders.
Aim 2.1: Determining the effect modifying role of exposure to concomitant medications on response to ARPI - We will perform a pooled analysis of these 6 trials to determine if the effect of ARPI on PFS and OS varies depending on receipt of concomitant medications during their treatment with ARPI.

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 on clinical prediction or risk prediction

Research Methods

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

Data source: Individual patient data from 6 randomized trials - TITAN trial (NCT02489318), LATITUDE (NCT01715285), COU-AA-301 (NCT00638690), COU-AA-302 (NCT00887198), ACIS (NCT02257736), SPARTAN (NCT01946204).
Inclusion Criteria:
All participants that were enrolled into one of those 6 trials and were randomly assigned to one of the two treatment arms, respectively.

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

Main Outcome Measures:
- Overall survival will be defined as the time from randomization to death from any cause.
- Progression-free survival as the time from randomization to the occurrence of radiographic progression, clinical progression, PSA progression, or death from any cause.

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

Eastern Cooperative group performance status, number of skeletal metastases, site of skeletal metastasis, Gleason score, presence of liver metastasis, worst pain score, albumin, lactate dehydrogenase (LDH), prostate-specific antigen (PSA), hemoglobin, prior LT, metastatic stage at presentation, tumor stage at diagnosis, nodal stage at diagnosis, and treatment regimen.

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

Baseline Factors:
- Ethnicity: Categorical
- Race: Categorical

- Age: Continuous
- height and weight: Continuous
- Nodal stage at presentation: categorical
- Prior prostate surgery or radiation therapy to prostate: yes/no (only for trials that had pre-treated prostate cancer patients)
- Date of prior prostate surgery (only for trials that had pre-treated prostate cancer patients)
- Date, and time-dose-fraction schedule of radiation therapy to prostate (only for trials that had pre-treated prostate cancer patients)
- Prior ADT (anti-androgen or Gonadotropin releasing hormone analogue) and duration
- Metastatic stage at presentation (only for trials that had pre-treated prostate cancer patients)
- ECOG PS: Ordinal (0-2)
- Tumor stage at diagnosis
- PSA at diagnosis
- Gleason score at diagnosis
- Date of randomization (date format) - to calculate PFS and OS

Baseline and Post-Baseline Variables:
- PSA: Continuous
- Hemoglobin: Continuous
- Serum albumin: Continuous
- Serum alkaline phosphatase: Continuous
- Serum LDH: Continuous
- Total WBC count with differential counts: Continuous
- Platelet count: Continuous
- Pain scores from brief pain inventory short form
- Patient reported quality of life (QoL) scores from FACT-P, EQ5D
- Cause of death
- - Life prolonging therapy received after progression

Statistical Analysis Plan:

The static risk prediction model built from LATITUDE trial (4), will be evaluated on the curated data from rest of the trials for OS and PFS. Model discrimination and calibration will be evaluated. The index of prediction accuracy will be used to compare the overall model performances. If this model fails to demonstrate satisfactory performance, a new model will be developed using both regression models (Cox and Fine-Gray regression) and statistical machine learning models (e.g., random forest survival and neural network). For modelling the association of dynamic changes in the serological biomarkers and patient reported QoL scores with OS, cancer-specific mortality, and PFS, we will apply a joint modelling framework which will link a linear mixed effect model (longitudinal submodel) and a Cox proportional hazard model (time-to-event submodel) through a shared random effect.
To determine the effect modifying role of prior prostate-directed local therapy and its type or exposure to concomitant medications on treatment effect from ARPI in advanced prostate cancer, we plan to focus specifically on the TITAN dataset. We will build multivariable Cox proportional hazard models separately for OS, radiographic progression-free survival, and cancer-specific mortality which will include an interaction term between receipt of prior local therapy with the randomized treatment regimen. Grambsch-Therneau test will be applied to check for violation of proportionality assumption and in presence of violation, weighted multivariable Cox regression will be applied. Similar approach will be used for determining the effect modifying role of type of prior local therapy and exposure to concomitant medications. The additional covariables in these models will include age, performance status on ECOG scale, PSA and Gleason score at enrollment, presence of visceral metastasis at enrollment, and tumor stage, Gleason score, metastatic stage, and PSA at presentation, respectively.

Software Used:

RStudio

Project Timeline:

- Project submission: March/April 2023

- Contract: May to July 2023
- Analysis: August 2023 to May 2024
- Abstract Submission (ESMO 2024): May 2024
- Paper Draft circulation: June 2024
- Paper Submission: July to September 2024

Dissemination Plan:

- Abstract presentation in ESMO 2024
- Submission of manuscript first-quartile oncology journals: Journal of Clinical Oncology, Journal of National Cancer Institute, JAMA Oncology, European Urology, Annals of Oncology.

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