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General Information

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/2024/03/coi_form_SM.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 - 212082PCR3011 - 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 - 56021927PCR3002 - 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)

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

Research Proposal

Project Title

Causal mediation role of prostate-specific antigen (PSA) and pain in metastatic hormone sensitive prostate cancer: a pooled analysis of 3 randomized controlled trials

Narrative Summary:

Prostate cancer is the most common cancer in the North American male population. In 2023, the

American Cancer Society estimates about 288,300 new cases of prostate cancer and about 34,700 deaths from prostate cancer. Of note, it is the second leading cause of cancer death in men in the U.S. after lung cancer. Approximately 3/4th of these patients are diagnosed when the prostate is still localized to the prostate gland. Majority of them receive curative local therapy including removal of the prostate or radiotherapy to the prostate. This is often combined with testosterone suppression as testosterone acts like a fuel for the prostate cancer cells and thus suppressing the testosterone inhibits growth of the cancer.

Despite these treatments, some of them progress to a phase where the cancer spreads to organs outside the prostate. Additionally, about 1/4th of patients are diagnosed when the cancer has already spread to other organs. As long as the cancer is responsive to testosterone suppression (lowering testosterone levels), metastatic prostate cancer patients are treated with testosterone suppression in combination with other drugs such as docetaxel which is a chemotherapy agent (a type or mixture of drugs that work by killing cancer cells), novel hormonal agents (drugs that work to slow or stop cancer growth by effecting hormone levels), or both.

Novel hormonal agents are first line treatment for these patients with metastatic hormone sensitive prostate cancer (mHSPC) after they were found to be the effective in a succession of randomized controlled trials which are a type of scientific experiment where people are randomly assigned to either a treatment group or a control group that doesn't receive the treatment. Darolutamide, Apalutamide, and Abiraterone are such novel hormonal agents, when added to testosterone suppression with or without docetaxel, a chemotherapy drug, was found to improve overall longevity in randomized controlled trials which are clinical studies where one treatment strategy is compared to the other in a large number of patients to choose the best strategy.

Prostate specific antigen is a marker for prostate cancer and increase or decrease in this marker, as detected by serial blood tests, corroborate with disease progression or regression in men with prostate cancer. However, it remains unknown if early PSA response plays a causal mediation role in the treatment effect on overall longevity. Similarly, longitudinal change in pain, as reported by patients, has been reported to be associated with outcome in metastatic prostate cancer. However, it remains unknown if pain progression could also play a causal mediating role in the treatment effect on overall longevity.

We propose a pooled analysis of three randomized controlled trials (ARASENS, LATITUDE, TITAN) to determine if early PSA drop and early pain progression (as defined in the trial) had any causal mediation role on the treatment effect from novel hormonal agents in conjunction with testosterone suppression with or without docetaxel on overall survival (OS). In other words, we would like to determine if PSA drop and pain progression could be some of the pivotal factors through which the combination of darolutamide, testosterone suppression, and docetaxel exerts its effect on OS. If found to be mediators, this will help us determine the possible outcome of patients early in the disease course and thereafter personalize their treatment accordingly.

Scientific Abstract:

Background: PSA response has been found to predict for improved outcome in patients with metastatic hormone sensitive prostate cancer (mHSPC) treated with ADT plus ARPI. However, it remains unclear if early PSA response played a causal mediating role on the treatment effect on OS and whether this mediating effect is differential between the two treatment groups. Association of early pain response with outcome has been demonstrated in a couple of secondary analysis of metastatic hormone refractory prostate cancer and mHSPC. However, it remains unknown if pain progression could play a causal mediation role on the treatment effect from triplet therapy on OS in mHSPC patients. Further, it remains unclear if slope of early dynamic change in PSA or patient reported pain predicts for OS in mHSPC patients treated with ADT and docetaxel with or without ARPI.

Objective: We propose a historical observational cohort study using individual patient data from

ARASENS, LATITUDE, TITAN to determine if early PSA response at or before 6 months or early pain progression at or before 6 months played an independent causal mediating role in treatment effect on OS. We also would evaluate if inter-patient difference slope of early dynamic change in PSA or pain within first 6 months after random assignment predicts for difference in OS.

Study Design: A pooled analysis using individual patient data from ARASENS (NCT02799602), TITAN (NCT02489318), and LATITUDE (NCT01715285), which are three multi-centric phase III double blinded placebo controlled randomized trials.
Participants:
Eligible patients will include mHSPC patients with metastases detected on conventional imaging. We will include all patients that were randomly assigned to any of the two randomized treatment regimens in each of the above three regimens, and had complete information on treatment, PSA response, pain progression (as defined by the trial), overall mortality, radiographic progression, and other baseline characteristics, respectively. We will pool ADT with or without docetaxel together given insignificant benefit of docetaxel over ADT alone based on recent network meta-analyses.

Primary and Secondary Outcome(s):
Main outcome: Overall survival (OS): OS will be determined as time from randomization to incidence of death from any cause. Alive patients will be censored at the date of last contact.

Secondary outcome(s): Time to PSA progression will be estimated using the trial definition and cumulative incidence of PSA progression will be estimated using deaths as competing risk event. Time to castrate resistance will also be included as a secondary outcome measure and will be defined based on trial definition.

Statistical Analyses:
We will compare the cumulative incidence of PSA progression considering deaths as competing risk events and will compare the incidence rates using Fine-Gray’s tests among early PSA responders versus non-responders across the treatment groups. We will explore if treatment effect on OS is mediated through early PSA nadir at 6 months after adjustment for exposures using causal mediation analysis methods suggested by VanderWeele et al. The mediation analysis will be adjusted for confounders that affect the mediator-outcome association. Direct counterfactual imputation estimation with bootstrap standard errors, bias-corrected and accelerated confidence intervals and p-values will be calculated. A multivariable Cox proportional hazard regression model will be applied to explore a continuous and potentially nonlinear relationship between time to early PSA response with OS in each treatment group where time to early PSA response will be fitted with restricted cubic splines. We will calculate inverse probability weighting (IPW) for adjusted OS estimates for those with and without early PSA response in the two treatment groups. If early PSA response is found to be a causal mediator of treatment effect on OS, we will train and validate a model to predict early PSA response at or before 6 months of random assignment. To determine the association of dynamic change in PSA or pain score (measured from The Brief Pain Inventory Short Form (BPI-SF)) with OS, we will apply separate Bayesian joint models to determine if inter-patient variation in the trajectory of dynamic changes in PSA or pain score until 6 months after random assignment predicted for OS.

Brief Project Background and Statement of Project Significance:

The combination of androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPI) with or without docetaxel is a standard-of-care systemic treatment strategy for men with metastatic hormone sensitive prostate cancer (mHSPC) based on a succession of large randomized controlled trials (Fizazi et al., 2021; Fizazi et al., 2021; Hussain et al., 2023; Smith et al., 2022; Chi et al., 2021; Fizazi et al., 2019; James et al., Armstrong et al., 2022, Attard et al., 2023). ARASENS, TITAN, and LATITUDE are some of these randomized controlled trials which have proven the efficacy of ARPI with or without docetaxel for men with mHSPC (Hussain et al., 2023; Smith et al., 2022; Chi et al., 2021; Fizazi et al., 2019). These trials have demonstrated OS advantages with darolutamide, apalutamide, and abiraterone, respectively when added to standard ADT (with or without docetaxel).

PSA response has been found to predict for improved outcome in patients treated with ADT plus

ARPI. In a post-hoc exploratory analysis of TITAN, Chowdhury et al. demonstrated that early PSA decline after random assignment was associated with significant improvement in rPFS and OS in patients treated with ADT plus apalutamide (Chowdhury et al., 2023). However, this study did not define the association of PSA kinetics with OS in the ADT alone arm. Similar findings were noted in a secondary analysis of the ADT plus Abiraterone arm of the LATITUDE trial (Matsubara et al., 2020). In a separate secondary analysis of SWOG 9346 that compared continuous versus intermittent ADT, Hussain et al. showed incremental OS benefit in patients with PSA <0.2 ng/mL and those with PSA of 0.2 ng/mL or higher but 4 ng/mL (Hussain et al., 2006). Finally, in a secondary analysis of ARASENS study, it was found that patients in the darolutamide arm who achieved undetectable PSA at 24 and 36 weeks had improved OS (HR [95% CI] 0.47 [0.35–0.63] and 0.37 [0.28–0.49]) and prolonged time to PSA progression (HR [95% CI] 0.28 [0.18–0.42] and 0.23 [0.15–0.34]), showing durable PSA response that was maintained over time (Saad et al., 2023). However, it remains unclear if early PSA response played a causal mediating role for the treatment effect from ADT plus ARPI (+/- docetaxel) on OS and whether this mediating effect is differential between the two treatment groups.

Association of early pain response with outcome has been demonstrated in a couple of secondary analysis of metastatic hormone refractory prostate cancer (Armstrong et al., 2007; Delanoy et al., 2019). In addition, a secondary analysis of LATITUDE trial shows a significant association of dynamic changes in patient reported pain with OS (Roy et al., 2023). However, it remains unknown if pain progression could play a causal mediation role on the treatment effect from triplet therapy on OS in mHSPC patients. Further, it remains unclear if slope of early dynamic change in PSA or patient reported pain predicts for OS in mHSPC patients treated with ADT and docetaxel with or without ARPI. Therefore, we propose a pooled analysis using individual patient data from ARASENS, LATITUDE, TITAN to determine if PSA response of ≤0.2 ng/mL at or before 6 months or early pain progression at or before 6 months played an independent causal mediating role for intensified hormonal manipulation (ARPI with ADT +/- docetaxel) effect on OS. We also would evaluate if inter-patient difference slope of early dynamic change in PSA or pain within first 6 months after random assignment predicts for difference in OS.

This pooled analysis will not only validate findings obtained from secondary analyses of individual studies, but also will validate the utility of early PSA response and early pain response as causal mediators for treatment effect from intensified hormonal manipulation on OS in mHSPC patients. A causal mediator is a variable that occurs in a causal pathway from an exposure (in this case treatment) to an outcome (in this case OS) and instead of a direct causal relationship between the exposure and outcome, a mediational model hypothesizes that the exposure variable causes the mediator variable, which in turn causes the outcome variable. We hypothesize that early PSA response and early pain progression are independent causal mediators of treatment effect ADT plus ARPI (with or without docetaxel) on OS. In other words, we would determine what extent of the treatment effect from ADT plus ARPI (with or without docetaxel) on OS is mediated through the treatment effect on early PSA response or early pain progression. If early PSA response and early pain progression are found to be causal mediators, this will enable us to personalize treatment early in the disease course which eventually will help improve outcomes in men with mHSPC. Further if early PSA response is found to be a causal mediator, our proposal will also provide a validated tool to predict early PSA response using baseline characteristics.

Specific Aims of the Project:

Specific Aim 1: Does early PSA response of ≤0.2 ng/mL at or before 6 months since random allocation plays a causal mediation role on the treatment effect on OS? We will determine the differect and indirec

Sub Aim 1.1: If time to early PSA response ≤0.2 ng/mL at or before 6 months has any association with OS?

Sub Aim 1.2: If we find early PSA response as a causal mediator, we plan to train and validate a model to predict early PSA response based on available baseline characteristics from the trials.

Specific Aim 2: Does early pain progression (as defined in the individual trials) at or before 6 months since random allocation plays a causal mediation role on the treatment effect on OS?

Objectives:
- We will determine if early PSA response of ≤0.2 ng/mL at or before 6 months played a mediating role on the treatment effect on OS and if there was a difference in the average causal mediation effect by PSA nadir varied between the two treatment groups (ADT with or without docetaxel versus ADT plus ARPI with or without docetaxel). A minimally sufficient set of confounders will be chosen to determine causal mediation role. We will model a non-linear relationship of time to early PSA response with OS in the pooled cohort. If early PSA response is found to be a causal mediator, we will train and validate a model based on baseline characteristics to predict early PSA response at or before 6 months.

- We will determine if early pain progression at or before 6 months played a mediating role on the treatment effect on OS and if there was a difference in the average causal mediation effect by PSA nadir varied between the two treatment groups. A minimally sufficient set of confounders will be chosen to determine causal mediation role.

- We will apply a joint model framework to determine if dynamic changes in the PSA or pain score or the slope of dynamic changes in the PSA or pain score was predictive of OS in patients with mHSPC. We will also determine if the association of dynamic changes in the PSA with OS varied between the two treatment arms.

Study Design:

Other

Study Design Explanation:

Causal mediation analysis from individual patient data from three randomized controlled trials

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

Other: Causal mediation analysis.

Research Methods

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

We propose a pooled analysis using individual patient data from ARASENS, TITAN, and LATITUDE, which are three multi-centric phase III double blinded placebo controlled randomized trials. In ARASENS (NCT02799602), 1306 patients with mHSPC (detected through conventional imaging) were randomly assigned to darolutamide versus placebo in conjunction with ADT plus docetaxel. A total of 651 patients were assigned to receive darolutamide and 655 patients were assigned to receive placebo, both in combination with androgen-deprivation therapy and docetaxel. In TITAN trial (NCT02489318), another multicentric phase III randomized trial, 1052 patients with mHSPC were randomly assigned to apalutamide versus placebo in conjunction with ADT with or without docetaxel. A total of 525 patients were assigned to receive apalutamide plus ADT and 527 to receive placebo plus ADT. In LATITUDE (NCT01715285), 1199 patients with de novo mHSPC patients were randomly assigned to abiraterone versus placebo in conjunction with ADT. Of these patients, 597 were assigned to the abiraterone group and 602 to the placebo group.

Eligible patients will include 18 years of age or older with an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1, histologically or cytologically confirmed prostate cancer, and metastases detected on bone scanning, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI). We will include all patients that were randomly assigned to any of the two randomized treatment regimens in each of the above three regimens, and had complete information on treatment, PSA response, pain progression (as defined by the trial), overall mortality, radiographic progression, and other baseline characteristics, respectively.

The patient data from ARASENS will be collected from the VIVLI platform and the overall analysis will be performed at the VIVLI platform.

Exclusion criteria: Not applicable.

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

Main outcome:
Overall survival (OS): OS will be determined as time from randomization to incidence of death from any cause. Alive patients will be censored at the date of last contact.

Secondary outcome(s):
Time to PSA progression will be estimated using the trial definition and cumulative incidence of PSA progression will be estimated using deaths as competing risk event. Time to castrate resistance will also be included as a secondary outcome measure and will be defined based on trial definition.

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

Primary Exposure:
Treatment arm: Categorical (ARPI plus ADT with/without docetaxel vs. ADT with/without docetaxel plus placebo)

Causal Mediators:
Early PSA response of ≤0.2 ng/mL at or before 6 months.
Pain progression at or before 6 months as defined in the trials.

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

- Age (in years) at the time of random assignment. Age could predict overall survival and could also predict PSA nadir (given elderly patients being less compliant to the treatment) and plays a confounding role.
- Gleason Score at initial diagnosis. Gleason score at diagnosis predicts the aggressiveness of the cancer and could predict outcome such as OS. Further aggressive cancers are less likely to have early PSA response. Thus, Gleason score is an important confounder.
- Eastern Cooperative Oncology Group Performance Status. ECOG Performance status is an independent predictor for overall survival in advanced prostate cancer patients and thus is pivotal to be added as a confounder.
- Prior Androgen Deprivation therapy (ADT): (yes/no). Prior ADT exposure could predict early PSA nadir (the causal mediator) and thus needs to be added as a confounder in the causal mediation model.
- Tumor stage at diagnosis: (T1 to T2 vs. T3 to T4). T-stage at diagnosis predicts the aggressiveness of the cancer and could predict outcome such as OS. Further aggressive cancers are less likely to have early PSA response. Thus T-stage is an important confounder.
- PSA at the time of trial enrolment (in ng/mL). Patients with higher baseline PSA are less likely to have early PSA nadir. Further baseline PSA could be a surrogate of baseline disease burden and thus could predict OS. Thus, baseline PSA is a confounder.

- Serial PSA data. This will help us determine who achieved early PSA response at or before 6 months. And this will be integral to the joint model approach of exploring the dynamic change in PSA with OS in the study population.
- Risk group per LATITUDE definition. LATITUDE risk group is predictive of OS and patients who belonged to high-risk group probably are less likely to attain early PSA nadir. Further, the PSA dynamics could be different between high and low risk patients. Similarly, the change in pain score could be different among the two subgroups. Thus, it is an important confounder.
- Volume of metastatic disease burden per CHAARTED definition. Volume of metastatic disease by CHAARTED definition is predictive of OS and patients who belonged to high volume group probably are less likely to attain early PSA nadir. Further, the PSA dynamics could be different between high and low volume patients. Similarly, the change in pain score could be different among the two subgroups. Thus, the volume of metastatic disease burden is an important confounder.
- Number of skeletal metastases. Number of skeletal metastases could be a predictor of dynamic change in pain score over time. Further, skeletal metastases burden could define outcome or OS in these patients. Patients with a higher number of skeletal metastases are less likely to have attained an early PSA nadir.
- Location of skeletal metastases (outside versus within pelvis or vertebral column). Location of skeletal metastases could be a predictor of dynamic change in pain score over time. Further, skeletal metastases outside pelvis or vertebral column predict poor OS. Further, these patients are less likely to have attained an early PSA nadir.
- Visceral metastasis (yes versus no). Patients with visceral metastasis have relatively poor prognosis; i.e., they have inferior OS. Further these patients are less likely to have an early PSA nadir or may have a different PSA trajectory than those without visceral metastasis.
- Nodal stage (N0 versus N1). The nodal stage at diagnosis is a predictor of overall survival. Further, patients with higher nodal burden are less likely to achieve an early PSA nadir or may have a slower overall decline in PSA.
- Serial pain scores as measured by Brief Pain Inventory–Short Form questionnaire. This will be pivotal for us to apply the longitudinal subcomponent of the Bayesian joint model wherein we are going to determine if inter-patient variation in the dynamic trajectory of pain score has an association with OS.

Statistical Analysis Plan:

We will compare the cumulative incidence of PSA progression considering deaths as competing risk events and will compare the incidence rates using Fine-Gray's tests among early PSA responders versus non-responders across the treatment groups. We will explore if treatment effect on OS is mediated through treatment effect on early PSA nadir by 6 months using causal mediation analysis (CMA) methods suggested by VanderWeele et al, 2011 i.e., decomposing the total treatment effect into direct and indirect effects. The CMA will be adjusted for confounders that affect the mediator-outcome association. Direct counterfactual imputation with bootstrapped standard errors, bias-corrected and accelerated confidence intervals will be calculated. We will pool ADT +/- docetaxel together given insignificant benefit of docetaxel over ADT alone based on recent network meta-analyses (Riaz et al., 2023, Roy et al., 2022). We will focus on total natural indirect effect, i.e., the effect of X on Y through M, when the direct effect is held constant at the treatment-group level X = 1 (ADT +/- docetaxel); TNIE = $E[Yi(1, Mi(1)) - Yi(1, Mi(0))]$, and the pure natural indirect effect, i.e., the effect of X on Y through M, when the direct effect is held constant at the control-group level X = 0 (ADT+/- docetaxel + ARPI); PNIE = $E[Yi(0, Mi(1)) - Yi(0, Mi(0))]$. We will also calculate proportion mediated which estimates the extent to which the mediating variable accounts for a total effect. A multivariable Cox proportional hazard model will be applied to explore a continuous and potentially nonlinear relationship between time to early PSA response with OS in each treatment group where time to early PSA response will be fitted with restricted cubic spline. We will calculate inverse probability weighting (IPW) for adjusted OS estimates for those with and without early PSA response in the two treatment groups. IPW-adjusted OS estimates will be also calculated for patients with PSA nadir of 0.2 ng/mL in the two treatment groups. A similar approach will be applied for causal mediation analysis for early pain progression by 6 months with OS. Further, to determine the association of dynamic change in PSA or pain score with OS, we will apply separate Bayesian joint models. A multivariable Cox proportional hazard regression model will be constructed for the time-to-event sub-model and a linear mixed-effects model will be built for the longitudinal sub-model. Time

of assessment will be included as random slope while patients will be included as random intercepts in the mixed model. The two sub-models will be linked through a shared random effect, often referred to as a current value association structure and its interaction with the randomized treatment regimen. Hazard ratio with 95% credible intervals will be reported from the Bayesian joint model.

If early PSA response is found to be a mediator in the causal pathway of treatment effect on OS, we will train and validate a model to predict early PSA response by 6 months of random assignment. We will select baseline characteristics available in the trial databases. An elastic net logistic regression model will be applied for variable selection and model training in the training data (after splitting the cohort into 70:30 ratio). Performance of the final model, including area under curve with 95% confidence intervals will be checked in the testing dataset. Further, bootstrapped calibration of the model will also be checked in the testing dataset.

In presence of missing data, we will perform 2 sensitivity analyses to determine the robustness of our findings. One will be a complete case analysis with multivariable Cox proportional hazard regression model (adjusting for confounders in anticipation of selection bias) while the other will be to perform the multivariable Cox proportional hazard model in a multiply imputed dataset. We will use R studio with its packages in VIVLI platform to perform the analyses.

Software Used:

RStudio

Project Timeline:

Proposal submission: March 28, 2024.
Proposal review and DUA execution: April to November 2024.
Data analysis start: December 21, 2024
Anticipated Data analysis completion: February 27, 2026.

Dissemination Plan:

- Abstract presentation in ASCO 2026- Submission of manuscript first-quartile oncology journals: Journal of Clinical Oncology, Journal of National Cancer Institute, European Urology, Annals of Oncology etc.

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