Principal Investigator

First Name: Soumyajit
Last Name: Roy
Degree: MBBS, MSc.
Primary Affiliation: Rush University Medical Center
E-mail: soumyajitroy8@gmail.com
State or Province: IL
Country: USA

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 by PSA and pain in metastatic hormone sensitive prostate cancer: a pooled analysis of 4 randomized controlled trials

Narrative Summary:

We propose a pooled analysis of 4 randomized controlled trials (ARASENS, LATITUDE, TITAN, and

ENZALUTAMIDE) 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 this combination exerts its effect on OS. If found to be mediators, this information will provide motivation for us to predict patients who could predict have early PSA drop or pain progression.

Scientific Abstract:

Background: Whether early PSA response or pain response is a causal mediator of treatment effect on OS in mHSPC patients, is largely unknown.
Objective: To determine if early PSA response at or before 6 months or early pain progression by 6 months played an independent causal mediating role in treatment effect on OS. We also would evaluate if 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), LATITUDE (NCT01715285), ENZAMET (NCT02446405).
Participants: Eligible patients will include mHSPC patients that were randomly assigned to any of the two randomized treatment regimens in the 4 trials.
Primary outcome: Overall survival (OS).
Secondary outcome(s): Time to PSA progression and time to castrate resistance.
Statistical Analyses: 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. The mediation analysis will be adjusted for confounders that affect the mediator-outcome association. 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. The model will be built using TITAN, LATITUDE, and ARASENS and then validate in ENZAMET trial. Bayesian joint model will be applied to determine association of dynamic change in PSA and pain with outcomes.

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 addition of ARPI to ADT (with or without docetaxel).

PSA response has been found to predict for improved outcome in patients treated with ADT plus ARPI(Chowdhury et al., 2023; Matsubara et al., 2020; Hussain et al., 2006; 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 outcomes secondary analysis of LATITUDE trial (Roy et al., 2023). However, it remains unknown if pain progression could play a causal mediation role on the treatment effect. Therefore, we propose a pooled analysis using individual patient data from ARASENS, LATITUDE, TITAN, ENZAMET to determine if PSA response of ≤0.2 ng/mL by 6 months or early pain progression by 6 months played an independent causal mediating role for intensified hormonal manipulation (ARPI with ADT +/- docetaxel) effect on 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. Further if early PSA response or pain progression 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 and pain progression by 6 months since random allocation plays a causal mediation role on the treatment effect on OS? We will decompose the total effect into direct and indirect effects to identify the mediation effect.
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. A similar approach will be used for pain progression.
Objectives:
- We will determine if early PSA response of ≤0.2 ng/mL by 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. 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. A similar approach will be used for early pain progression.

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 and model building and validation

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 4 randomized controlled trials. In ARASENS (NCT02799602), 1306 mHSPC patients were randomly assigned to darolutamide versus placebo with ADT plus docetaxel. In TITAN trial (NCT02489318), 1052 patients with mHSPC were randomly assigned to apalutamide versus placebo with ADT with or without docetaxel. In LATITUDE (NCT01715285), 1199 patients with de novo mHSPC patients were randomly assigned to abiraterone versus placebo with ADT. In ENZAMET (NCT02446405), 1125 patients were randomly assigned to ADT with or without enzalutamide with or without docteaxel. Eligible patients will include patients with histologically confirmed prostate cancer, and metastases detected on conventional imaging. We will include all patients that were randomly assigned to any of the two randomized treatment arms and had complete information on outcomes and variables of interest including baseline and post-baseline PSA and pain response. Patients with no post-baseline PSA or pain score will be excluded. ARASENS will be delivered on VIVLI and author has ENZAMET data which will be uploaded to VIVLI where the analyses will be done.

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.
- Gleason Score at initial diagnosis.
- Eastern Cooperative Oncology Group Performance Status.
- Prior Androgen Deprivation therapy (ADT): (yes/no).
- Tumor stage at diagnosis: (T1 to T2 vs. T3 to T4).
- PSA at the time of trial enrolment (in ng/mL).
- Serial PSA data (baseline and post baseline)
- Risk group per LATITUDE definition.
- Volume of metastatic disease burden per CHAARTED definition.
- Number of skeletal metastases.
- Location of skeletal metastases (outside versus within pelvis or vertebral column).
- Visceral metastasis (yes versus no).
- Nodal stage (N0 versus N1).
- Serial pain scores as measured by Brief Pain Inventory–Short Form questionnaire (baseline and post-baseline).

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. If found to be a causal mediator we will build a model to predict early PSA response. These models will be built based on TITAN, ARASENS, and LATITUDE and validated using ENZAMET trial.

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: November 8, 2024.
Proposal review and DUA execution: November 20, 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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