Principal Investigator

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General Information

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Prostate Cancer Foundation Young Investigator Award (23YOUN21)
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/02/SV_57KskaKADT3U9Aq-R_6Qufzw17g4BqnaN.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. NCT01088529 - A Randomized, Open-Label, Neoadjuvant Prostate Cancer Trial of Abiraterone Acetate Plus LHRHa Versus LHRHa Alone
2. NCT01790126 - The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men With Biochemically Relapsed Hormone Sensitive 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

Does prostate-specific membrane antigen (PSMA) predict prostate tumor response to androgen deprivation therapy (ADT) and androgen receptor signaling inhibitors (ARSIs) in previously untreated disease?

Narrative Summary:

Prostate cancer aggressiveness varies widely, making biomarker assessment crucial for prognosis. Clinicians typically use PET imaging based on the tumor’s expression of a protein called PSMA.

However, not all prostate cancers expression PSMA. Our study focuses on two trials (NCT01088529, NCT01790126) where patients received hormone therapy pre-surgery. We'll analyze RNA profiles of prostate tumors pre-therapy, correlating PSMA RNA levels with clinical outcomes. This will enhance understanding of PSMA's predictive role in hormone therapy response.

Scientific Abstract:

Background: Prostate cancer (PC) aggressiveness is heterogeneous – necessitating avenues for personalizing care.
Objective: To correlate clinical outcomes with PSMA RNA levels in prostate tumors prior to treatment with hormonal therapy.
Study Design: Post-hoc analysis of two trials of patients with prostate cancer who received hormonal therapy prior to prostatectomy.
Participants: Patients in NCT01088529 or NCT01790126 who also had RNA profiling of their prostate tumors prior to hormonal therapy.
Primary and Secondary Outcome Measure(s):

NCT01790126: 1) Time to PSA progression, 2) proportion of patients without evidence of PSA or radiographic progression in the setting of recovered serum testosterone (≥150 ng/dL) at 24 months, and 3) proportion of patients with PSA <0.2 ng/mL after 7 months of therapy.

NCT01088529: 1) ypT2N0, 2) three measures of tumor quantity at prostatectomy (volume, cell density, and epithelium volume), and 3) 3-year recurrence-free survival.

Statistical Analysis: Multivariable Cox regression for time-to-event analyses and multivariable logistic regressions for dichotomous outcomes. PSMA RNA abundance will be categorized as high (above median) vs low (below median).

Brief Project Background and Statement of Project Significance:

Prostate cancer (PCa) is extremely common and biologically diverse - necessitating avenues to advance precision care. PET imaging based on the cell surface marker PSMA has become more commonly used to better characterize PCa and has been approved by the FDA and guidelines for early-stage disease. We hypothesize that PSMA RNA abundance as a proxy for uptake on PSMA PET positively correlates with response to hormone therapy. Our ongoing work suggests treatment naïve tumors high in PSMA also have higher androgen receptor signaling and patients with tumors high in PSMA also have better oncologic outcomes when treated with hormone therapy.

If this analysis shows PSMA RNA abundance can help identify patients who respond best to hormone therapy it would suggest that PSMA PET metrics could be leveraged to individualize management for future patients with PCa and optimize accrual for clinical trials assessing hormone therapies. Because PSMA PET will become increasingly obtained for early-stage disease, PET imaging could become one of the most commonly obtained biomarkers for PCa treatment decision making.

Specific Aims of the Project:

1) Correlate clinical outcomes with PSMA RNA abundance in patients treated with neoadjuvant hormonal therapy in NCT01790126. We hypothesize that patients with high intratumoral PSMA RNA abundance have better clinical outcomes in response to hormonal therapy compared to those with low PSMA RNA abundance.

2) Correlate clinical outcomes with PSMA RNA abundance in patients treated with neoadjuvant hormonal therapy in NCT01088529. We hypothesize that patients with high intratumoral PSMA RNA abundance have better clinical outcomes in response to hormonal therapy compared to those with low PSMA RNA abundance.

Study Design:

Individual trial analysis

What is the purpose of the analysis being proposed? Please select all that apply.

Confirm or validate previously conducted research on treatment effectiveness

Research Methods

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

Inclusion: All patients in either NCT01790126 or NCT01088529 who received the study treatment and surgery.

Exclusion: Missing data on RNA abundance in prostate tumors prior to hormone therapy. Missing data on clinical variables such as patient age and tumors grade and stage. Missing data on follow-up for all time-to-event analyses.

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

Only time to PSA progression will be assessed as a time-to-event analysis. The remaining outcomes will be assessed as dichotomous outcomes.

NCT01790126
Primary: Time to PSA progression

Secondary:
1) proportion of patients without evidence of PSA or radiographic progression in the setting of recovered serum testosterone (≥150 ng/dL) at 24 months, and 2) proportion of patients with PSA <0.2 ng/mL after 7 months of therapy.

NCT01088529:
Primary: ypT2N0

Secondary:
1) three measures of tumor quantity at prostatectomy (volume, cell density, and epithelium volume), and 2) 3-year recurrence-free survival.

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

The main independent variable will be PSMA RNA abundance. PSMA RNA abundance will be categorized as high (above median) vs low (below median) within each trial.

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

Other variables to include in multivariable analyses will be patients age (Continuous per 10-year increase), tumor grade group (1-3 vs 4-5), tumor stage prior to surgery (T1-2 vs 3-4), and tumors size prior to surgery (per 1 cm increase).

Statistical Analysis Plan:

We propose to leverage these clinical data and the RNA profiles to test our hypothesis. We would first stratify patients by high (above median) and low (below median) of PSMA RNA abundance (FOLH1). For the time-to-event outcomes (Outcome 1 Aggarwal et al.) we would conduct a multivariable Cox regression adjusting for treatment arm and the high vs. low PSMA RNA abundance (FOLH1). For the dichotomous outcomes (all others), we would perform multivariable logistic regressions adjusting for treatment arm and PSMA RNA abundance as a continuous variable. We would graphically present these data with Kaplan-Meier curves for the time-to-event outcome. For the other analyses, we would use box plots to plot the unadjusted PSMA levels by outcome.

Software Used:

RStudio

Project Timeline:

Once we obtain data access, we hope to take 3 months analyzing the data. We then predict it will take another 2 months for manuscript drafting, and 6 more months for submission and publication.

Dissemination Plan:

We will propose to submit the data from these trials in abstract form to the 2024 annual meeting of the society of urologic oncology which will take place December 4-6, 2024 in Dallas Texas. We will also plan to submit this work along with ongoing work in a manuscript targeted for a translational oncology research audience.

Bibliography:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7205516/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9534720/