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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/2019/08/coi_julian_ch_-_co_i.pdf
https://yoda.yale.edu/wp-content/uploads/2016/12/coi_rob_hamilton.pdf
https://yoda.yale.edu/wp-content/uploads/2020/06/yoda_coi_-_lajkosz.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 - 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)
2. NCT01946204 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men With Non-Metastatic (M0) Castration-Resistant Prostate Cancer
3. 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)

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

Research Proposal

Project Title

Statin use and outcomes in patients treated in the SPARTAN, TITAN and ACIS trial

Narrative Summary:

There is increasing interest in statin medications as inhibitors of prostate cancer (PCa) initiation and progression. Studies have shown positive associations between statin use and PCa outcomes, though nearly all have been retrospective. We will evaluate the association between statin use and outcomes in both arms of the SPARTAN, TITAN and ACIS study. We anticipate the results of this study will add rationale to explore statin use in combination with androgen axis inhibition (and in particular Apalutamide) in a prospective clinical trial in the nmCRPC, mHSPC and mCRPC setting, and further our understanding of statin synergies in PCa biology.

Scientific Abstract:

Background:There is increasing interest in statin medications as inhibitors of prostate cancer (PCa) initiation and progression.
Objective: We will evaluate the association between statin use and outcomes in both arms of the SPARTAN study, the TITAN study and the ACIS study.
Study Design: Using a list of confounders, we will calculate a propensity score for statin use using a logistic regression model. For each statin user, match 2 non-statin users using the nearest neighbour matching algorithm with a caliper width of 0.2 times the standard deviation of the propensity scores. To ensure the cohort is well-matched, plot the propensity score distribution between the statin and non-statin users, and review the standardized differences of each characteristic between statin and non-statin users. Potential confounders will be: Age, Gleason Score, ECOG, Baseline PSA, Alkaline Phosphatase, LDH, Opiate use, Geographic region, Metastasis stage at initial diagnosis (TITAN, ACIS), Visceral disease and bone metastasis at baseline (TITAN, ACIS), docetaxel status.
Participants: All 1,207 patients from the SPARTAN trial will be eligible for the study. The 982 patients from the ACIS trial will be eligible for the study, and all 1,052 patients from the TITAN trial will also be eligible for the study.
Primary and Secondary Outcomes:
Primary outcomes: Radiographic progression-free survival (rPFS), Overall survival for TITAN and ACIS, and Metastases-free survival (MFS) in the SPARTAN trial
Secondary outcomes:
1. Time to initiation of cytotoxic chemotherapy
2. Time to pain progression
3. Time to opioid use
4. Time to skeletal-related event
5. Time to PSA progression
6. Second progression free survival
7. Time to symptomatic local progression

Statistical analysis: To assess the impact of statin use for each outcome, plot two Kaplan-Meier curves for each outcome, the first stratifying results by statin use (i.e. all patients), and the second stratifying results by statin use and treatment arm (Apalutamide vs. placebo OR Apalutamide + Abiraterone vs Abiraterone) . Use the log-rank test to compare the survival curves. Report the 1, 2, and 3-year survival probabilities along with their 95% confidence intervals. Report the median survival and its 95% confidence interval where applicable.
Additionally, a multivariate Cox proportional hazards model will be fit for each outcome using the propensity-matched cohort. To account for the matched nature of the data, stratify the model on the matched groups. The following model compositions will be considered:
1. Statin use (reference group = non-users)
2. Statin use + treatment arm (reference group = placebo arm)
3. Statin use + treatment arm + statin x treatment interaction
Depending on the distribution of confounders in the propensity-matched cohort, other confounders may need to be added to the Cox models. Finally, analyses will be done by statin type and dose/duration if that information is available. For statin type, depending on the distribution of statins used the analysis maybe bivariate (hydrophilic vs. hydrophobic) or will be done by specific type (e.g. atorvastatin vs. simvastatin etc.).
Subgroup Analyses: To explore the impact of statin, use and Apalutamide within subgroups, the statistical analyses described previously will be repeated for all subgroups defined for each study (SPARTAN, TITAN and ACIS). Only the primary endpoints accordint to each study will be examined.

Brief Project Background and Statement of Project Significance:

There is increasing interest in statin medications as inhibitors of prostate cancer (PCa) initiation and progression. Studies have shown positive associations between statin use and PCa outcomes, though nearly all have been retrospective[1?3]. In very advanced settings, such as metastatic castrate resistant prostate cancer (mCRPC), the data are conflicting. For example, in a large retrospective study of mCRPC patients receiving enzalutamide or abiraterone after treatment with docetaxel, a positive association of statin use with overall- and cancer-specific survival was observed[4]. On the contrary, Harshman et al., and Boegemann et al., did not observe an OS benefit associated with statin use among mCRPC patients treated with abiraterone[5,6]
It may be that in earlier disease settings, where survival times are longer, more of a benefit attributable to statin use would be observed. For example, in our secondary analysis of the PR7 randomized trial of intermittent vs. continuous androgen deprivation therapy in men with biochemical recurrence, statin use was associated with a reduced risk of overall (HR: 0.64; 95% C.I. 0.53-0.78, p

Specific Aims of the Project:

We will evaluate the association between statin use and outcomes in both arms of the SPARTAN, TITAN and ACIS studies.
Objective: To explore potential additive effect of statins on Apalutamide efficacy in patients with nmCRPC, mHSPC, and mCRPC
Hypothesis: We hypothesized that statin users treated with Apalutamide or Apalutamide + Abiraterone will have improved outcomes compared to nonusers.

Study Design:

Individual trial analysis

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:

All 1,207 patients from the SPARTAN trial will be eligible for the study.
All 982 patients from the ACIS trial will be eligible for the study
All 1,052 patients from the TITAN trial will also be eligible for the study.
Exclusion: Unavailable information regarding the primary exposure: Statin use at baseline vs. no statin use at baseline.

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

SPARTAN trial:
Primary outcome: Metastases-free survival, as defined in the SPARTAN trial
Secondary outcomes:
1. Time to metastasis as defined in the SPARTAN trial
2. Progression-free survival, as defined in the SPARTAN trial
3. Time to symptomatic progression as defined in the SPARTAN trial
4. Time to initiation of cytotoxic chemotherapy as defined in the SPARTAN trial
5. Overall survival
6. Time to PSA progression as defined in the SPARTAN trial and according to the PCWG2
7. Second-progression-free survival as defined in the SPARTAN trial
TITAN trial
Primary outcomes: Radiographic progression-free survival (rPFS), as defined in the TITAN trial, Overall survival as defined in the TITAN trial
Secondary outcomes:
1. Time to initiation of cytotoxic chemotherapy as defined in the TITAN trial
2. Time to pain progression as defined in the TITAN trial
3. Time to opioid use as defined in the TITAN trial
4. Time to skeletal-related event as defined in the TITAN trial
5. Time to PSA progression as defined in the TITAN trial
6. Second progression free survival as defined in the TITAN trial
7. Time to symptomatic local progression as defined in the TITAN trial

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

Statin use at baseline vs. no statin use at baseline.

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

TITAN
1. Age (continuous)
2. Gleason Score
3. ECOG performance status
4. Baseline PSA (continuous)
5. Alkaline Phosphatase (continuous)
6. LDH (continuous)
7. Opiate use (yes vs. no)
8. Geographic region
9. Metastasis stage at initial diagnosis (M0 vs M1)
10. Visceral disease and bone metastasis at baseline (Yes vs No)
11. Previous docetaxel (yes vs. no)
12. Disease Volume: (Low volume disease vs High volume) as defined in the TITAN trial
SPARTAN
1. Age (continuous)
2. Gleason Score

3. ECOG performance status
4. PSA doubling time (continuous)
5. Use of bone-sparing agent (yes vs. no)
6. Classification of local or regional disease (N0 vs N1)
7. Previous prostate cancer treatment (Prostatectomy or radiation therapy vs Gonadotropin-releasing hormone analogue agonist vs first generation antiandrogen agent)
8. Race/ethnic group
9. Geographic region
10. Number of previous hormonal therapies
11. Baseline PSA (continuous)
ACIS
IDEM +
10. Sites of disease at baseline: (Bone only, lymph node, soft tissue, visceral)
11. Tumor stage at diagnosis
12. Lymph node stage at diagnosis
13. Metastasis stage at diagnosis
14. Bone lesions at baseline (?10 vs >10)

Statistical Analysis Plan:

Propensity Matching
Using all confounders listed before (Variables of interest), we will calculate a propensity score for statin use using a logistic regression model. For each statin user, match 2 non-statin users using the nearest neighbour matching algorithm with a caliper width of 0.2 times the standard deviation of the propensity scores. To ensure the cohort is well-matched, plot the propensity score distribution between the statin and non-statin users, and review the standardized differences of each characteristic between statin and non-statin users.
To assess the impact of statin use for each outcome, plot two Kaplan-Meier curves for each outcome, the first stratifying results by statin use (i.e. all patients), and the second stratifying results by statin use and treatment arm (Apalutamide vs. placebo OR Apalutamide + Abiraterone vs. Abiraterone). Use the log-rank test to compare the survival curves. Report the 1, 2, and 3-year survival probabilities along with their 95% confidence intervals. Report the median survival and its 95% confidence interval where applicable.
Additionally, a multivariate Cox proportional hazards model will be fit for each outcome using the propensity-matched cohort. To account for the matched nature of the data, stratify the model on the matched groups. The following model compositions will be considered:
1. Statin use (reference group = non-users)
2. Statin use + treatment arm (reference group = placebo arm)
3. Statin use + treatment arm + statin x treatment interaction
Depending on the distribution of confounders in the propensity-matched cohort, other confounders may need to be added to the Cox models. Finally, analyses will be done by statin type and dose/duration if that information is available. For statin type, depending on the distribution of statins used the analysis maybe bivariate (hydrophilic vs. hydrophobic) or will be done by specific type (e.g. atorvastatin vs. simvastatin etc.).
Subgroup Analyses
To explore the impact of statin use and Apalutamide within subgroups, the statistical analyses aforementioned will be repeated for all subgroups below (TITAN). Only the primary endpoints rPFS and OS will be examined.
1. Baseline PSA above median: Yes, No
2. ECOG score at baseline: 0, 1
3. Age: 7
8. Previous docetaxel use: Yes, No
9. Baseline LDH above ULN: Yes, No
10. Baseline ALP above ULN: Yes, No
11. Disease volume: High, Low
12. Metastasis stage at initial diagnosis: M0, M1
For SPARTAN The subgroups, derived from Smith et al[14], are as follows: Baseline PSA doubling time: >6 months, ?6 months.

1. Use of bone-sparing agent: yes, no
2. PSA level at baseline: At or below median, above median
3. Age

Software Used:

R

Project Timeline:

After data acquisition we anticipate 2-3 months of analysis time, and an additional 2-3 months to prepare a final manuscript. Manuscript submission and acceptance could take an additional 3-5 months depending on reviewers? feedback. Thus, the total estimated project length is 6-11 months from the time of data acquisition.

Dissemination Plan:

As we successfully have done previously with other projects, we intend presentations at intramural, local, national and international symposia in GU cancers, and survivorship. This research will produce three different manuscripts and are suitable for publication in high impact journals such as Journal of Urology, European Urology, European Urology Oncology.

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Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2023/07/2023-5274-Additional-Information-23-09-29.docx