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General Information

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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?: Conference

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2018_3.pdf
https://yoda.yale.edu/system/files/tianjings_form.pdf
https://yoda.yale.edu/system/files/hwanhees_form.pdf
https://yoda.yale.edu/system/files/otiss_form2.pdf
https://yoda.yale.edu/system/files/channings_form2.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
Associated Trials:

1. NCT01314118 - 212082PCR2005 - A Multicenter, Open-label, Single-arm, Phase 2 Study of Abiraterone Acetate Plus Prednisone in Subjects With Advanced Prostate Cancer Without Radiographic Evidence of Metastatic Disease

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

Research Proposal

Project Title

The relative efficacy and safety of enzalutamide, apalutamide, abiraterone, and darolutamide for nonmetastatic castration-resistant prostate cancer

Narrative Summary:

Recently, there has been progress in research in nonmetastatic castration-resistant prostate cancer (nmCRPC) treatment, with the introduction of several promising drugs. The multitude of treatment options complicates decision-making, as little is known about the optimal drug therapy, which is reflected in the hesitance in clinical guidelines to recommend one drug over the others. With the comparative efficacy and safety of different drugs unclear, the costs of those drugs vary widely. In this study, we seek to compare the efficacy and safety of enzalutamide, apalutamide, abiraterone, and darolutamide for nmCRPC through network meta-analysis that incorporates individual patient trial data.

Scientific Abstract:

Background: Recently, there has been progress in research in nonmetastatic castration-resistant prostate cancer (nmCRPC) treatment, with the introduction of four promising drugs, namely, apalutamide, enzalutamide, abiraterone , and darolutamide. The multitude of treatment options complicates decision-making, as little is known about the optimal drug therapy for each disease status, which is reflected in the hesitance in clinical guidelines to recommend one drug over the others. With the comparative efficacy and safety of different drugs unclear, the costs of those drugs vary widely. The monthly costs range from around $3,275 to $12,196 for different drugs
Objective: To compare the efficacy and safety of enzalutamide, apalutamide, abiraterone, and darolutamide for nmCRPC.
Study design: A systematic review and network meta-analysis of randomized controlled trials and single-arm trials, incorporating individual patient trial data. We will identify trials from searching bibliographic databases, trial registries, and regulatory documents.
Participants: nmCRPC patients
Main Outcome Measures: 1. Time to radiographic progression or death from any cause, which ever occurred first. 2. time to PSA progression. 3. overall survival.4. adverse events.
Statistical Analysis: Network meta-analysis by Bayesian hierarchical model using generalized linear modeling and Markov Chain Monte Carlo (MCMC) methods. We will estimate the relative treatment effect between any two drugs and use the Surface Under the Cumulative RAnking curve (SUCRA) as well as mean ranks to compare drugs.

Brief Project Background and Statement of Project Significance:

Recently, there has been progress in research in nonmetastatic castration-resistant prostate cancer (nmCRPC) treatment, with the introduction of four promising drugs, namely, apalutamide, enzalutamide, abiraterone , and darolutamide.[1-8] The availability of these drugs has improved prostate cancer survival. Meanwhile, the multitude

of treatment options complicates decision-making, as little is known about the optimal drug therapy, which is reflected in the hesitance in clinical guidelines to recommend one drug over the others.[9-11]
With the comparative efficacy and safety of different drugs unclear, the costs of those drugs vary widely. The monthly costs range from around $3,275 to $12,196 for different drugs. [12] Considering the huge disparity in costs, it is critical to evaluate the relative efficacy and safety of these drugs and inform value-based decision-making. Are higher costs justified by better treatment effects or a better safety profile? Or is there actually no difference, making abiraterone is the most economic choice?
In this study, we seek to compare the efficacy and safety of alternative drug therapies for nmCRPC in order to inform decision-making. We will identify, appraise, and synthesize data from clinical trials of drug therapies for nmCRPC with network meta-analysis that incorporates individual patient trial data, a state-ofart statistical method that has recently risen to prominence in comparative effectiveness research.

Specific Aims of the Project:

Objective: To compare the efficacy and safety of enzalutamide, apalutamide, abiraterone, and darolutamide for nonmetastatic castration-resistant prostate cancer through network meta-analysis of clinical trial data.
Hypothesis: some drug therapies may be more efficacious or safer than other drug therapies.

What is the purpose of the analysis being proposed? Please select all that apply.
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

We will identify trials and obtain aggregated level trial data from searching bibliographic databases, trial registries, and regulatory documents. We will request individual patient trial data from trial data sharing websites including Vivli and YODA. Currently, we are in the process of requesting individual patient data of two trials (NCT00626548 and NCT01664923) from Vivli. The request ID is 00003762.

***IMPORTANT NOTES: For details of potential challenges in securing individual patient trial data and solutions, see the additional file uploaded

We will include nmCRPC patients from randomized controlled trials that compared apalutamide, enzalutamide, abiraterone, or darolutamide, in combination with androgen deprivation therapy with any comparators, or from single-arm trials that examined any of the four drug therapies.

Main Outcome Measure and how it will be categorized/defined for your study:

Efficacy:
1. Primary outcome: time to radiographic progression (local or distant) or death from any cause, which ever occurred first.
2. Secondary outcome: time to PSA progression; overall survival.
For time-to-event outcomes, the number of patients who had the event, the median follow-up time, median survival, and the hazard ratio will be extracted.
Safety:
1. Number of patients included in safety analysis;
2. Any adverse events, serious adverse events, or treatment discontinuation due to adverse events.
For the dichotomous outcomes, the number of patients had the event will be extracted.

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

Drug therapy: apalutamide, enzalutamide, abiraterone, darolutamide, or placebo/no treatment.

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

Age (continuous), serum prostate-specific antigen (PSA) level (continuous), PSA doubling time (continuous), Gleason category (categorical), previous local therapy for prostate cancer (categorical), performance status (continuous).

Statistical Analysis Plan:

We will conduct network meta-analysis under a Bayesian framework using generalized linear modeling and Markov Chain Monte Carlo (MCMC) methods. The dichotomous outcomes will be determined by using an odds ratio (OR) with 95% credible intervals (CI). The time-to-event outcomes will be determined by using a hazard ratio (HR) with 95% CI. As the dosages for our alternative drug therapies are established, we expect little or no variation and will combine different dosage if necessary. We will estimate the relative treatment effect between any two drugs and use the Surface Under the Cumulative RAnking curve (SUCRA) as well as mean ranks to compare drugs.
Software Used:
RStudio
Project Timeline:

Anticipated project start date: June 2019
Analysis completion date: June 2020
Manuscript drafted: December 2020
First submission: January 2021
Results reported back to the YODA project: March 2021

Dissemination Plan:

Products: A manuscript to be published in major oncology journals (Journal of Clinical Oncology, JAMA Oncology, etc).
Audiences: Clinicians, patients, health policy makers, and health researchers.

Bibliography:

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12. Drug Price Information. https://www.drugs.com/price-guide/

Supplementary Material:

https://yoda.yale.edu/sites/default/files/potential_challenges_in_securing_ipd_and_solutions.docx