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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: NCI Cancer Center Support Grant 5P30CA056-036 and DOD Data science award
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/nikita_coi_yoda.pdf
https://yoda.yale.edu/system/files/coi_for_yoda_lu-yao.pdf
https://yoda.yale.edu/system/files/yoda_keithcoi.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. NCT00638690 - COU-AA-301 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
2. NCT0087198 - COU-AA-302 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer
3. NCT00924469 - COU-AA-201-DFCI - A Phase 2 Open-Label, Randomized, Multi-center Study of Neoadjuvant Abiraterone Acetate (CB7630) Plus Leuprolide Acetate and Prednisone Versus Leuprolide Acetate Alone in Men With Localized High Risk Prostate Cancer
4. NCT01088529 - COU-AA-203 - A Randomized, Open-Label, Neoadjuvant Prostate Cancer Trial of Abiraterone Acetate Plus LHRRa Versus LHRRa Alone
5. NCT0142930 - 212082PCR2008 - An Open-Label Study to Determine the Short-Term Safety of Continuous Dosing of Abiraterone Acetate and Prednisone in Modified Fasting and Fed States to Subjects With Metastatic Castration-Resistant Prostate Cancer
7. NCT01695135 - ABI-PRO-3001 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
8. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant Prostate Cancer
9. NCT00473512 - COU-AA-001 - A Phase I/II Open Label Study of the 17α-Hydroxylase/ C17,20 Lyase Inhibitor, Abiraterone Acetate in Patients With Prostate Cancer Who Have Failed Hormone Therapy
10. NCT00474383 - COU-AA-003 - A Phase II Open Label Study of CB7630 (Abiraterone Acetate) in Patients With Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy
11. NCT00485830 - COU-AA-004 - A Phase II Open Label Study of CB7630 (Abiraterone Acetate) and Prednisone in Patients With Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy
12. NCT01695135 - ABI-PRO-3001 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) and Prednisolone in Patients With Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy.
13. NCT01795703 - JNJ-212082-JPN-202 - A Phase II Study of JNJ-212082 (Abiraterone Acetate) in Metastatic Castration-Resistant Prostate Cancer Patients Who Have Received Docetaxel-based Chemotherapy
14. NCT00473746 - COU-AA-002 - Phase II/II Open Label Dose Escalation Study of the 17α-Hydroxylase/ C17,20 Lyase Inhibitor, Abiraterone Acetate in Hormone Refractory Prostate Cancer
15. NCT01795703 - JNJ-212082-JPN-202 - A Phase II Study of JNJ-212082 (Abiraterone Acetate) in Metastatic Castration-Resistant Prostate Cancer Patients Who Have Received Docetaxel-based Chemotherapy
16. NCT00544440 - COU-AA-BMA - An Observational Study of Continuous Oral Dosing of an Irreversible CYP17 Inhibitor, Abiraterone Acetate (CB7630), in Castration-Resistant Prostate Cancer Patients Evaluating Androgens and Steroid Metabolites in Bone Marrow Plasma
17. NCT01867710 - 212082PCR2023 - A Randomized Phase 2 Study Evaluating Abiraterone Acetate With Different Steroid Regimens for Preventing Symptoms Associated With Mineralocorticoid Excess in Asymptomatic, Chemotherapy-naïve and Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients
18. 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)

18. NCT01591122 - ABI-PRO-3002 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer

19. NCT02257736 - 56021927PCR3001 - 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)

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

Research Proposal

Project Title

Risk of therapy-related adverse events in men on abiraterone or enzalutamide, a meta-analysis of clinical trial data

Narrative Summary:

Prostate cancer (PCa) is the most common cancer and second leading cause of male death. Patients receive first generation androgen deprivation therapy (ADT) first-line and have a higher risk of therapy-related adverse events (TRAEs) compared to those not on these agents as well as men without PCa. The addition of newer agents may increase TRAEs. 4-6 TRAEs vary between drugs; enzalutamide (ENZ) has increased hypertension while abiraterone (ABI) increases other risks. 5,7-11 No clear guidance exists on newer drugs’ use nor the role of functional status on safety. This study will compare the safety and efficacy of ENZ and ABI for metastatic castration resistant PCa through meta-analysis.

Scientific Abstract:

Background: Prostate cancer (PCa) is the second leading cause of male death; over 260,000 men are diagnosed and 35,000 die each year. Patients receive first generation androgen deprivation therapy (ADT) first-line and have a higher risk of therapy-related adverse events (AEs), including cardiovascular disease (CVD) outcomes. The introduction of androgen receptor targeted (ART) drugs to ADT may increase therapy-related AE and CVD risk. There is no recommendation in clinical guidelines to choose one drug over the other, and the choice of treatment options complicates clinical decision-making. This trial will offer a comparison of ABI and ENZ to improve clinician decision-making and enhance patient care. Is there a difference in outcomes according to patient type based on drug received?

Objective: To compare the safety of enzalutamide and abiraterone for mCRPC.

Study design: Individual participant data (IPD) systematic review and meta-analysis of randomized controlled trials and single-arm trials, according to PRISMA-IPD best practices. 12 Trials identified in trial repositories.

Participants: mCRPC patients

Main Outcome Measures: 1. Therapy-related adverse events 2. Time to radiographic progression or death from any cause, which ever occurred first. 3. Time to PSA progression. 4. Overall survival.

Statistical Analysis: We will conduct IPD meta-analysis utilizing a two-stage approach as discussed by Walker et al13 and espoused by the Cochrane Individual Participant Data Meta-analysis Methods Group. 14 Stage one will include a summary of each individual trial. Stage two will involve a meta-regression stratified by study type using mixed effects modeling techniques with structures that account for the relative similarity (i.e., correlation) of observations within the same study by random effects when we generalize effect estimation and inference across studies by fixed effects comparing the exposure of interest (the independent variable, abiraterone and enzalutamide). This methodology will also serve to maintain the overall structure of the individual studies, as they will not be treated as an overall aggregate and analyzed as though they were drawn from a single study and ostensibly independent and identically distributed (iid) observations. The dichotomous outcome effects will be estimated by odds ratios (OR) with 95% credible intervals (CI). The time-to-event outcome effects will be estimated by hazard ratios (HR) with 95% CI.
Brief Project Background and Statement of Project Significance:

Prostate cancer (PCa) is the most common cancer and second leading cause of death among men; over 260,000 men are diagnosed yearly and nearly 35,000 will die from the disease. Patients receive first generation androgen deprivation therapy (ADT). ADT blocks the secretion of testosterone and other androgens and is first-line therapy. PCa patients are at increased risk of therapy-related adverse events (TRAEs), including cardiovascular disease (CVD) outcomes. ADT works to decrease the growth of the prostate tumors by decreasing androgen. The introduction of newer agents called androgen receptor targeted (ART) drugs to ADT may further increase therapy-related AE and CVD risk. ARTs work in two ways, either by blocking the site on the tumor so it cannot receive androgens depriving the tumor of androgens or by stopping androgen production; both means decrease a tumor’s ability to grow. TRAEs vary between drugs; enzalutamide (ENZ) has increased hypertension while abiraterone (ABI) has shown increased CVD risk. Currently, there is no clear recommendation in clinical guidelines to utilize one drug over the other, and the choice of treatment options complicates clinical decision-making. In this study, we seek to compare the safety and efficacy of alternative ARTs for mCRPC in order to inform decision-making. We will identify, appraise, and synthesize data from clinical trials of two current therapies for mCRPC with two-stage meta-analysis incorporating individual participant data in line with PRISMA-IPD best practices. Increasing guidance to clinician decision-making enhances patient care. The question to answer: is there a difference in outcomes according to patient type based on drug received? Alternatively, are the outcomes similar for all patients regardless of drug choice?

Specific Aims of the Project:

Aim: To compare the therapy-related AE outcomes of enzalutamide and abiraterone for metastatic castration-resistant prostate cancer through individual participant data (IPD) meta-analysis of clinical trial data.

Hypothesis: Enzalutamide will have lower AE and CVD risk than abiraterone in mCRPC patients.

What is your Study Design?:

Meta-analysis (analysis of multiple trials together)

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

- Confirm or validate previously conducted research on treatment safety
- Participant-level data meta-analysis
- Meta-analysis using data from the YODA Project and other data sources

Research Methods

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

Eligibility for trials
- Study designs: RCTs or single-arm trials.
- Participants: included mCRPC patients.
- Interventions: enzalutamide or abiraterone in combination with ADT.
- Comparators: any comparators or single-arm trials with no comparator.
- Outcomes: reported efficacy and safety outcomes. The main outcome measure is time to and frequency of grade 3 or 4 therapy-related adverse events.
- Timing and setting: median duration of follow-up more than 12 months; any setting.
- Language and year: English language; year since 2011- abiraterone was approved in 2011, enzalutamide in 2012.
- Enzalutamide RCTs (NCT02384382, NCT02215096, NCT01664923, NCT01212991, NCT02485691) to be requested from Vivli (Request ID# 8688) and analysis to be conducted under Vivli-YODA agreement at Vivli secure platform. See attachment for description of enzalutamide studies.
Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

1. Primary outcome: time to and frequency of grade 3 or 4 therapy-related adverse events.

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

Drug category: abiraterone, enzalutamide, 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:

Composite of four cardiovascular risk and mortality outcomes (dichotomous); acute myocardial infarction events (count), heart failure events (count), cardiovascular related deaths (dichotomous), and non-cardiovascular related deaths (dichotomous);
Age (continuous), race (categorical), prostate specific antigen (PSA) level (continuous), PSA density (continuous), PSA doubling time (continuous), Gleason category (categorical), previous therapy for PCa (categorical), performance status (categorical)

Statistical Analysis Plan:

Eligibility for trials
Study designs: RCTs or single-arm trials. Phase I trials, cross-over trials, cluster RCTs, or quasi-randomized trials will be excluded.

Participants: included mCRPC patients.

Interventions: enzalutamide or abiraterone in combination with ADT.

Comparators: any comparators or single-arm trials with no comparator.

Outcomes: reported efficacy and safety outcomes. The main outcome measure is time to and frequency of grade 3 or 4 therapy-related adverse events.

Timing and setting: median duration of follow-up more than 12 months; any setting.

Language and year: English language; year since 2011- abiraterone was approved in 2011, enzalutamide in 2012.

Ways to handle missing data:
We will contact principle investigators for missing data. And in case where missing data were not because of the reporting of trial results but because of loss-to-follow up or data collection issues, we will use multiple imputation to address missing data in covariates and outcomes.

Ways to handle differences in outcome measures: we specified our primary and secondary outcomes based on a preliminary search and review of eligible trials. We selected outcomes that are consistently reported across trials.

Ways to handle the differences in study designs: we limited eligible trials to randomized controlled trials and single-arm trials with at least 12 months of median follow-up time. As the drug dosage and regimen are established for the drug therapies of interest, we expect little variation in terms of the administration of intervention. Statistically, we will use random effects model to account for heterogeneity in study results derived from different study designs.

We will conduct IPD meta-analysis utilizing a two-stage approach as discussed by Walker et al13 and espoused by the Cochrane Individual Participant Data Meta-analysis Methods Group. Stage one will include a summary of each individual trial. Stage two will involve a meta-regression stratified by study type using mixed effects modeling techniques with structures that account for the relative similarity (i.e., correlation) of observations within the same study by random effects when we generalize effect estimation and inference across studies by fixed effects thus comparing the exposure of interest (the independent variable, abiraterone and enzalutamide). This methodology will also serve to maintain the overall structure of the individual studies, as they will not be treated as an overall...
aggregate and analyzed as though they were drawn from a single study and ostensibly independent and identically distributed (iid) observations. 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.

**Software Used:**

R

**Project Timeline:**

Anticipated project start date: February 2023  
Analysis completion date: January 2024  
Manuscript drafted: June 2024  
First submission: July 2024  
Results reported back to the YODA project: September 2024

**Dissemination Plan:**

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

**Bibliography:**


**Supplementary Material:**