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General Information

Key Personnel (in addition to PI):

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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?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/coi_klara.pdf

https://yoda.yale.edu/system/files/coi_tobias.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. [NCT00887198 - 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](#)

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

Research Proposal

Project Title

Quality-of-life in men with castration-resistant prostate cancer treated with enzalutamide or abiraterone: a systematic review with meta-analyses

Narrative Summary:

We summarize previous literature on patients experience with the two hormonal therapies, enzalutamide and abiraterone, against prostate cancer. Both treatments have separately been thoroughly studied. Both treatments inhibit prostate cancer equally well and both treatments are generally well-tolerated.

We want to compare previous literature on the effects of enzalutamide and abiraterone on quality of life in men with prostate cancer. The aim of this research is to guide treatment choice to improve patients' treatment experience in the future.

Scientific Abstract:

Background

Enzalutamide and abiraterone acetate plus prednisolone (AAP) are standard first-line treatments for men with metastatic castration-resistant prostate cancer (mCRPC), with similar efficacy but different side effects (1–4). The subjective patient experience has been reported in randomised controlled trials, finding an improvement in health-related quality-of-life (HRQoL) of men treated with enzalutamide and AAP (5,6). These trials did not compare the treatments head to head and an updated systematic review of the treatments' effect on HRQoL is lacking to guide treatment choice (7–9).

Objective and aim

This is a systematic review with meta-analyses of patient reported HRQoL, in men with mCRPC treated with first-line enzalutamide or AAP. The aim is to guide treatment choice.

Study design

The study design is a systematic review with meta-analyses, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (10). The protocol is registered on PROSPERO with registration number: CRD42019127143.

Participants

We included studies with participants treated with first-line mCRPC treatment with AAP or enzalutamide.

Main Outcome Measure.

The main outcome is the change in the questionnaire FACT-P total score, from baseline to 12-week follow-up, of clinical trials on men treated with first-line enzalutamide, AAP or placebo for mCRPC.

Statistical Analysis – meta-analyses.

The mean change and mean treatment difference (with 95 % confidence interval (CI)) in FACT-P total score will be analysed in meta-analyses.

Brief Project Background and Statement of Project Significance:

Enzalutamide and abiraterone acetate plus prednisolone (AAP) are standard first-line treatments for men with metastatic castration-resistant prostate cancer (mCRPC), with similar efficacy but different side effects (1–4). Even though many of the adverse events are similar, others are different: enzalutamide is associated with memory impairment and seizures, while AAP is associated with liver function abnormalities, peripheral oedema and cardiac events (1,4,11). In addition to these objectively observed side-effects, the subjective patient experience has also been reported: randomised controlled trials have shown an improvement in health-related quality-of-life (HRQoL) of men treated with enzalutamide and AAP (5,6). These trials did not compare the treatments head to head. The only direct comparison to date is a recent randomised clinical trial that demonstrated AAP to be associated with better HRQoL than enzalutamide in men over the age of 75 years (12). The effect of enzalutamide and AAP on HRQoL

have been compared in systematic reviews, but they did either only include placebo-controlled trials, not report HRQoL in men on first-line treatment or not include the most recent publications(7–9). Therefore, an updated comparison of Enzalutamide and AAP effects on HRQoL is needed to guide the treatment choice to improve the patient's treatment experience. We aim to publish the results of this systematic review in a peer-reviewed international journal and that the results will be presented at national and international conferences and symposiums to enhance medical knowledge.

Specific Aims of the Project:

The objective with the systematic review with meta-analyses is to compare effects on patient reported quality of life in men treated with abiraterone and enzalutamide. The aim is to guide treatment choice to improve the patients' treatment experience. The primary hypothesis is that patients treated with abiraterone have increased health-related quality of life while patients treated with enzalutamide have reported decreased health-related quality of life at 12-week follow-up. The secondary hypothesis is that patients reported better HRQoL after treatment with abiraterone than enzalutamide.

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

Summary-level data meta-analysis

Summary-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:

Data Source

The following databases were searched: Medline via Pubmed, Embase via Ovid, Cochrane Systematic Reviews, clinicaltrials.gov and clinicaltrialsregister.eu

Inclusion/Exclusion Criteria

Systematic review

We included peer reviewed prospective studies of patient reported health-related quality-of-life (HRQoL), assessed by questionnaires, in men treated with enzalutamide or abiraterone acetate and prednisone (AAP) as first-line metastatic castration-resistant prostate cancer (mCRPC) treatment, published in English, Danish, Swedish or Norwegian. Patient reported HRQoL assessed by questionnaires was defined as total and subscale results from validated questionnaires assessing health-related, general, cancer specific and prostate cancer specific quality-of-life, depression, cognitive function, pain and fatigue.

We excluded case reports, case series, unpublished research and studies with fewer than 25 participants receiving first-line mCRPC treatment with abiraterone or enzalutamide.

Meta-analyses

The inclusion criteria for the meta-analyses were clinical trials that assessed HRQoL by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score.

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

The main outcome is the change in patient-reported health-related quality of life, assessed with the questionnaire FACT-P, in men treated with abiraterone or enzalutamide. The main outcome is defined as the mean change with 95 % CI in FACT-P total score, from baseline to 12-week (+/- 1 week) follow-up, in clinical trials on men treated with first-line enzalutamide, AAP or placebo for mCRPC. The results from different studies will be presented in a table and will be used in meta-analyses of a systematic review. Two meta-analyses will be made. First, the change in FACT-P total score, from baseline to 12-week follow-up, will be pooled for trials on abiraterone and enzalutamide separately. Secondly, the difference in FACT-P total score between patients treated with enzalutamide or abiraterone, will be compared indirectly in a net-work meta-analysis.

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

The first meta-analysis:

Dependent variable: treatment group (abiraterone group)

Independent variable: Change in FACT-P total score from baseline to 12-weeks follow-up (mean change with 95 % CI of the abiraterone treatment arm)

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

Second meta-analysis (net-work meta-analysis):

Dependent variable: treatment group (treatment with abiraterone, enzalutamide or placebo)

Independent variable: treatment difference in changed FACT-P total score from baseline to 12-week follow-up (the difference in the mean change with 95 % CI for the abiraterone group and for the placebo group)

Statistical Analysis Plan:

As I wrote to the corresponding author of the publication, entitled: "Repeated measures analysis of patient-reported outcomes in prostate cancer after abiraterone acetate". I would like to include results from this paper in a meta-analysis on health-related quality of life in men treated with abiraterone. Currently, I can only estimate the results required for the meta-analysis from a figure in the publication (figure 2, page 152).

I kindly wonder if I could get following results from the COU-AA-302 trial's mixed models for repeated measures (MMRM) analyses:

The mean change with 95% CI in FACT-P total score, from baseline to cycle 3 (84 days), in the abiraterone-prednisone treatment arm.

The mean change with 95% CI in FACT-P total score, from baseline to cycle 3 (84 days), in the prednisone-alone treatment arm.

The results will be presented in a table. We will also compare the changed health-related quality of life in men treated with enzalutamide or abiraterone, from clinical trials measuring health-related quality of life with the FACT-P questionnaire, in two different meta-analyses. First, the mean change with 95 % CI (from baseline to 12-week (+/- 1 week) follow-up) in FACT-P total score, analysed with MMRM, for each treatment group (abiraterone and enzalutamide) will be pooled in separate generic inverse variance forest plots.

Secondly, enzalutamide and abiraterone will be compared indirectly in a net-work meta-analysis. Data used in the net-work meta-analysis is the difference in FACT-P total score between active treatment and placebo and if applicable between enzalutamide and abiraterone. Fixed effect analysis model will be used if the heterogeneity is less than 50 % and random effects will be used if heterogeneity is more than 50%.

Software Used:

I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform

Project Timeline:

Project start: the literature search begun March 2019.

Estimated analysis completion date: February 2020.

Estimated drafted manuscript: February 2020

Estimated first submission date: March 2020

Estimated date results are reported back to Yoda: March 2020, if the manuscript is accepted for review in March 2020.

Dissemination Plan:

The anticipated product is a systematic review manuscript with meta-analyses. The targeted audience are Urologist, Oncologist and others with a background in medical science and an interest in advanced metastatic prostate cancer. European Urology Oncology is a potentially suitable journal for submission of the completed research project.

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