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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/06_-_yoda_conflict_of_interest.pdf
https://yoda.yale.edu/system/files/conflict_of_interest_riemer.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. 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
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 LHRHa Versus LHRHa Alone
5. NCT01424930 - 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
6. 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
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 17?-Hydroxylase/ C17,20 Lyase Inhibitor, Abiraterone Acetate in Patients With Prostate Cancer Who Have Failed Hormone Therapy
10. NCT00485303 - 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
11. NCT01685983 - 212082PCR2007 - A Phase 2 Open Label Study of Abiraterone Acetate (JNJ-212082) and Prednisolone in Patients With Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy.
12. 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
13. NCT00473746 - COU-AA-002 - Phase I/II Open Label Dose Escalation Study of the 17?-Hydroxylase/ C17,20-Lyase Inhibitor, Abiraterone Acetate in Hormone Refractory Prostate Cancer
14. 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
15. 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
16. 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

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

Research Proposal

Project Title

Psychiatric Symptoms as Adverse Events of Abiraterone / Prednisolone Therapy: Systematic Review and Meta-Analysis

Narrative Summary:

Older anti-androgen treatment option haven been frequently associated with psychiatric adverse events such as depression, anxiety, and loss of libido. In contrast, the novel anti-androgen Abiraterone does not seem to cause psychiatric adverse events with none being reported in any of the product informations (Zytiga,Abiratas, Abretone, Abirapro). The aim of this study is to systematically review studies employing Abiraterone/Prednisolone in patients with prostatic cancer and to analyse whether or not there is a risk for psychiatric adverse events. Adverse events of interest include but are not limited to anxiety, depression, and insomnia.

Scientific Abstract:

Background: Metastasized prostate carcinoma is one of the most frequent diseases of geriatric males. Among the treatment option are anti-androgens such as Flutamide, Enzelutamide, or Cyproteron acetate. These drugs have been frequently associated with psychiatric adverse events. The novel anti-androgen Abiraterone does not seem to cause psychiatric adverse events. Objective: The aim of our study is to systematically review all available studies employing Abiraterone in patients with metastasized prostate carcinoma, to extract data for psychiatric adverse events such as anxiety, depression, and insomnia, and to analyze both qualitatively and quantitatively whether or there is a particular risk for these events. Study Design: Our study is a systematic review and meta-analysis of both published and unpublished data on patients with prostate carcinoma who received anti-androgen therapy with Abiraterone. Studies are collected after a literature search in two scientific databases (PubMed, WebOfScience) and two Clinical Trial Registries (EudraVigilance, ClinicalTrials). Data from unpublished studies are sought out by contacting study authors or manufacturers. Total numbers of exposed patients and frequencies of psychiatric and psychosomatic adverse events of these patients are extracted, categorized, and reviewed. Participants: No one, because it is a Review. Main Outcome: Frequencies for psychiatric or psychosomatic adverse events for Abiraterone. Statistical Analysis: For placebo-controlled studies, meta-analyses are calculated for adverse events during Abiraterone vs. Placebo.

Brief Project Background and Statement of Project Significance:

Abiraterone is a novel anti-androgen drug which is used in the treatment of metastasized prostate carcinoma. In contrast to older anti-androgens Abiraterone is not an antagonist on androgen receptors but rather inhibits the synthesis of androgens, estrogens, and glucocorticoids. As reported in product information, therapy with Abiraterone does not cause psychiatric or psychosomatic adverse events unlike the older anti-androgens. Our project is to evaluate the risk of psychiatric or psychosomatic by the means of a systematic review and meta-analysis. If the results of our independent study confirm the safety of Abiraterone regarding mental health, it may help raise awareness of the suitability of Abiraterone therapy in patients with prostate carcinoma and comorbid psychiatric disorders of vulnerability towards a psychiatric disorder.

Specific Aims of the Project:

Aim of our project is to systematically investigate and review whether a therapy with Abiraterone / Prednisolone is associated with psychiatric adverse events. Product information mentions only non-psychiatric adverse events during a treatment with Abiraterone / Prednisolone. If we can support this with evidence, Abiraterone should be superior as older anti-androgens in patients with comorbid psychiatric disorder or a vulnerability towards a psychiatric disorder. Our hypothesis is that based on the occurrence of psychiatric symptoms in older anti-androgens, Abiraterone / Prednisolone should also cause psychiatric symptoms. To evaluate or hypothesis we will extract data on psychiatric (including psychosomatic) adverse events from interventional and observational studies using Abiraterone / Prednisolone, determine their frequencies across studies, and meta-analytically compare the frequencies of psychiatric adverse events during Abiraterone / Prednisolone to those during placebo.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safety
Confirm or validate previously conducted research on treatment safety
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
Other

Research Methods

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

For the literature search, we used two databases (PubMed/MEDLINE and WebOfScience) and two clinical trials registries (EudraVigilance and ClinicalTrials). Keyword for research was „Abiraterone“ without further restrictions. Selection of literature was performed manually using pre-defined criteria. We included observational and

interventional trials on male, human subjects with prostate carcinoma with at least one treatment arm of Abiraterone / Prednisolone that reported at least one psychiatric adverse events.
Terms which represent psychiatric adverse events and we are interested in, are the following: "Asthenia", "Fatigue", "Anorexia", "Loss of Appetite", "Decreased Appetite", "Depression", "Insomnia", "Anxiety", "Somnolence", "Depressed Mood", "Delirium", "Confusional State", "Confusion", "Metal Status Change", "Hallucination", "Loss of Libido", "Decreased Libido", "Mood Swings", "Amnesia", and/or "Psychiatric Disorder".

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

Our study investigates frequencies of psychiatric adverse events during treatment with Abiraterone / Prednisolone in all included studies. All randomized, placebo-controlled studies will be part of meta-analysis.

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

For the review, the predictor for the outcome of interest is treatment with Abiraterone / Prednisolone. For the meta-analysis, the predictor for the outcome of interest is treatment (with Abiraterone / Prednisolone vs. Placebo).
Terms which represent psychiatric adverse events and we are interested in to conduct the frequencies of, are the following: "Asthenia", "Fatigue", "Anorexia", "Loss of Appetite", "Decreased Appetite", "Depression", "Insomnia", "Anxiety", "Somnolence", "Depressed Mood", "Delirium", "Confusional State", "Confusion", "Metal Status Change", "Hallucination", "Loss of Libido", "Decreased Libido", "Mood Swings", "Amnesia", and/or "Psychiatric Disorder".

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

Frequencies of the following specified psychiatric advers events symptoms: "Asthenia", "Fatigue", "Anorexia", "Loss of Appetite", "Decreased Appetite", "Depression", "Insomnia", "Anxiety", "Somnolence", "Depressed Mood", "Delirium", "Confusional State", "Confusion", "Metal Status Change", "Hallucination", "Loss of Libido", "Decreased Libido", "Mood Swings", "Amnesia", and/or "Psychiatric Disorder".

Statistical Analysis Plan:

In the systematic review, data will be analyzed qualitatively. In the meta-analysis, odds-ratios will be calculated for the different adverse effects occurring under Abiraterone / Prednisolone vs. Placebo using RevMan 5.
Software Used:
I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform
Project Timeline:

Our project is nearly finished. All aforementioned databases and clinical trial registries were searched and the studies were scanned, categorized and analyzed. Frequencies were extracted and evaluated. We also contacted several authors of studies that did not report adverse events in their publications. The requested studies in YODA is the last in our attempt to gain a most complete set of data.

Project start date: 01.04.2019
Analysis completion date: 15.10.2019 (but still waiting for additional and more detailed data from YODA)
Manuscript drafted date: 01.04.2019
Publication date: 01.06.2019
Results reported back date: 28.20.2020

Dissemination Plan:

Our project is part of a master thesis for a M.Sc. in Psychology. A condensed version of the thesis is also going to be published in a journal focusing either on urology or geriatric psychiatry. Potential journals are: "Der Urologe (The Urologist)" and "Aktuelle Urologie (Actual Urology)". But we also want to try to publicate first in "The Uropean Journal of Urology".
If submission is succesfull you will receive a copy of the manuscript.

Bibliography:

A short selected enumeration of included studies:

- de Bono et al. (2011) / NCT00638690
- Fizazi et al. (2017) / NCT01715285
- Ryan et al. (2013) / NCT00887198
- Ye et al. (2017) / NCT01591122
- Attard et al. (2018) / NCT01995513
- Clarke et al. (2018) / NCT01972217
- de Bono et al. (2019) / NCT01485861
- Smith et al. (2019) / NCT02043678
- Attard et al. (2019) / NCT01867710
- Chi et al. (2013) / NCT01681433
- Madan et al. (2012) / NCT01553188
- Stein et al. (2018) / NCT02737332
- Sydes et al. (2018) / NCT00268476
- Szmulewitz et al. (2018) / NCT01543776