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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

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2017-signed_fankhauser.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2017_-_gerke.pdf
http://yoda.yale.edu/system/files/coi_jc.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 Trial(s):

1. NCT00638690 - 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 - 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

Do alpha blockers and 5?-reductase inhibitors influence survival and urinary function in patients with castration resistant prostate cancer?

Narrative Summary:

Many patients who were prescribed alpha blockers or 5-ARI because of lower urinary tracts symptoms continue to take those drugs when they are diagnosed with prostate cancer or castration resistant prostate cancer (CRPC) even though little is known about the clinical impact of those drugs in the CRPC setting. Therefore it is of utmost importance to clarify the combination of alpha blockers or 5-ARI with abiraterone, which is a novel anti hormonal treatment option for patients with CRPC. The aim of this study is to observe the influence of alpha blockers or 5-ARI on progression free and overall survival as well as on urinary function using trial data for patients treated with abiraterone.

Scientific Abstract:

Background
Many patients who were prescribed alpha blockers or 5-ARI because of lower urinary tracts symptoms (LUTS) continue to take those drugs when they are diagnosed with prostate cancer or castration resistant prostate cancer (CRPC) even though little is known about the clinical impact of alpha blockers or 5-ARI in the CRPC setting. Therefore it is of utmost importance to clarify the combination of those drugs with abiraterone.
Objective
To assess the association between 5-ARI intake and PFS, OS and need for palliative TURP, ureter stent placement and change in urinary symptoms or incidence of urinary tract infections
Study Design
Post-hoc analysis of two randomized controlled phase 3 studies.
Participants
Patients treated with abiraterone in the chemotherapy-naïve and post-chemotherapy CRPC setting.
Main Outcome Measures
Radiographic progression free and overall survival as well as on urinary function
Statistical Analysis
Uni- and multivariable Cox regression analysis, Kaplan–Meier plots and log-rank tests

Brief Project Background and Statement of Project Significance:

Prostate cancer (PC) is one of the most common cancers in men leading to an estimated 1.1 million new diagnoses every year and is the second leading cause of male cancer mortality in western countries with more than 200,000 PC deaths every year [1]. When PC is limited to the prostate, cure can be achieved by either surgery or radiotherapy. However, in patients with metastases, cure is usually no longer possible. Patients with advanced PC are typically treated with androgen deprivation therapy (ADT) because PC growth is dependent on androgens (i.e. testosterone), which bind to the androgen receptor (AR) of the PC cell. However, PC cells eventually adapt to the low testosterone levels leading to disease progression despite androgen deprivation. This state of the disease is termed castration-resistant PC (CRPC). Nevertheless, recurrent tumors frequently express androgen receptor (AR) [2] or downstream target genes, such as prostate-specific antigen (PSA) [3], and many patients with CRPC respond to second line hormonal treatment options including abiraterone (Abi) or enzalutamide (Enza) [5, 6]. These findings suggest that CRPC cells are neither hormone refractory nor androgen independent and maintain a clinically relevant reliance on the AR signaling axis and 5?-reductase inhibitors (5-ARI) inhibitors may play a role in

cancer progression because of 2 modes of action.
First, 5-ARI inhibit the conversion of testosterone to the more potent dihydrotestosterone and may influence disease progression. Especially because a proposed mechanism of resistance includes AR activation by androgens converted from adrenal androgens or synthesized within the cancer cell itself, 5-ARI may have an effect on disease progression [13].
Second, by controlling conversion to subsequent metabolites of Abi and Enza it seems plausible that 5-ARI inhibitors improve the response to second line hormonal treatment options. Abi is converted into several metabolites, of which some have anti- and others show pro-tumor activity. As a first step Abi is converted to D4A, which blocks multiple enzymes required for 5?-dihydrotestosterone (DHT) synthesis, antagonizes the androgen receptor (AR), and has more potent anti-tumour activity than Abi itself[7]. Subsequently D4A is irreversibly converted into 6 different metabolites summarized as 5?- and 5?- metabolites which have either pro- or antitumor activity[8]. In a clinical trial the addition of a 5?-reductase inhibitor led to an accumulation of the anti-tumor metabolite D4A and a depletion of the pro-tumor 5?-abiraterone metabolites [8, 9]. Similarly, the combination of a 5?-reductase inhibitor and Enza compared to Enza alone led to a more pronounced inhibition of cell proliferation compared to Enza alone [10].
Many patients who were prescribed 5-ARI because of lower urinary tracts symptoms (LUTS) continue to take alpha blockers or 5-ARIs when they are diagnosed with PC or CRPC even though little is known about the clinical impact of those drugs in the CRPC disease settings. Therefore it is of utmost importance to clarify the combination of alpha blockers or 5-ARI with Abi.

Specific Aims of the Project:

Specific Aim: To evaluate the impact of alpha blockers and 5?-reductase inhibitors (5-ARI) on radiographic progression free (rPFCS) and overall survival (OS) as well as on urinary function in patients treated with abiraterone because of castration resistant prostate cancer
Null hypothesis: No difference in rPFS, OS and urinary function between patients with or without 5-ARI
Hypothesis: Patients with treated with 5-ARI show superior rPFS, OS and urinary function

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:

Inclusion criteria: Patients treated with abiraterone within the COU-AA-301/302 trials
Exclusion criteria: Radical prostatectomy

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

- Progression free survival (PFS) and overall survival (OS)
- Time to palliative TURP because of urinary tract obstruction
- Time to double-J stent placement because of ureteral obstruction
- Change of urinary symptom scores according to FACT Advanced Prostate Symptom Index (FAPSI)

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

Age
BMI
ECOG performance status
Patient reported outcomes
Time since diagnosis
PSA at study inclusion
Presence of visceral metastases
Lactate dehydrogenase
Opioid analgesic use
Average baseline pain score (based on Brief Pain Inventory question 3
Baseline fatigue severity (based on Brief Fatigue Inventory question 3

Albumin
Hemoglobin
Alkaline phosphatase
Number of bone metastases at screening
Type of disease progression at study entry
Number of prior chemotherapy regimens
Duration of prior hormonal use
Treatment of primary tumor
Subsequent treatment

Statistical Analysis Plan:

We perform univariable Cox regression analysis to assess the association between 5-ARI intake and PFS, OS and need for palliative TURP, ureter stent placement and change in urinary symptoms. Multivariable Cox regression analyses including potential confounders will be performed to control for potential bias. Kaplan–Meier plots and log-rank tests will used to compare the outcomes of interest between patients with or without alpha blocker or 5-ARI usage.

Project Timeline:

Access to data 01/2018
Statistical anaylsis 01-06/2018
Manuscript writing 07-09/2018
Submission 10/2018

Dissemination Plan:

Journal of clinical oncology
Jama oncology
European Urology

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