## Principal Investigator

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## General Information

**Key Personnel (in addition to PI):**
**First Name:**
**Last name:**
**Degree:**
**Primary Affiliation:**
**SCOPUS ID:**

**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

http://yoda.yale.edu/system/files/coi_davidlorente.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

Clinical Significance and Factors Associated with PSA Progression in mCRPC Patients Treated with Abiraterone

**Narrative Summary:**

Asessment of treatment efficacy in metastatic castration-resistant prostate cancer is commonly based on a composite endpoint including PSA, radiographic and clinical progression.1 Despite the use of PSA response as a secondary endpoint in most trials, the clinical significance of a PSA progression is unclear, especially in the absence of clinical/radiographic progression. Most trials did not mandate treatment discontinuation in this scenario. We aim to evaluate the clinical significance of PSA progression in abiraterone-treated patients in the COU-AA-301/302 trials,2,3 in order to identify patients at a high risk of clinical or radiographic progression before clinical deterioration ensues.

**Scientific Abstract:**

Background: abiraterone acetate (AA) has been shown to prolong survival in two large randomized trials in mCRPC patients. In both trials, patients experiencing PSA progression (PSAprog) exclusively were allowed to continue on treatment. Rates of PSA only progression in abiraterone-treated patients have not been reported, and its prognostic significance remains unknown.

Objective: to evaluate the incidence, prognostic significance and factors associated with PSAprog in mCRPC patients treated with AA/placebo + prednisone.

Study Design: retrospective cohort study.

Participants: mCRPC patients treated in the COU-AA-301 and COU-AA-302 trials, with a baseline and at least one post-treatment PSA value.

Main Outcome Measures: Overall survival.

Statistical Analysis: The proportion of patients experiencing primary, secondary PSAprog and PSA-only progression will be calculated. Uni- and multivariable Cox proportional hazards models will be used to evaluate the association of PSAprog and OS, rPFS, cPFS and time to QoL deterioration. Time from PSAprog only to radiographic/clinical progression or death will be calculated. Uni- and multivariable Cox proportional hazards (PH) models will be used to evaluate factors associated with time to rPFS / cPFS in patients with PSAprog only. Known prognostic clinical factors will be included as covariates in each of the Cox-PH models. The performance of the models will be evaluated by calculating the c-indices. Analyses will be performed in all subjects, and separately in the abiraterone and placebo-treated cohorts.

**Brief Project Background and Statement of Project Significance:**

Although an isolated PSA progression (without radiographic or clinical progression) is accepted as an entry criterion for clinical trials, PCWG3 guidelines do not mandate treatment discontinuation with PSA progression. Similarly, clinical guidelines do not recommend treatment discontinuation based on PSA progression exclusively in daily clinical practice;4,5 generally, continuation until the occurrence of radiographic or clinical progression is recommended. These recommendations are not based on prospective data evaluating the value of a rising PSA on treatment. Furthermore, factors influencing the time between PSA and radiographic/clinical progression are largely unknown.

Most analyses have focused on the survival advantage of patients experiencing a PSA decline on treatment.6,7 A number of different studies have established a favourable outcome for patients experiencing 30% or 50% PSA declines. PSA response, however, has failed to meet the Prentice Criteria and has therefore not qualified as a surrogate for overall survival.8

The prognostic significance of a rise in PSA, either as a primary rise (at 12 weeks after treatment initiation) or as a secondary progression (after a previous PSA decline) is less well studied. PSA progression at a landmark 3 or 7-month time point has been associated with a worse outcome in chemotherapy-treated patients in two randomized clinical trials.9 In an single-centre study of abiraterone-treated patients, PSA progression as early as 4 weeks after treatment initiation was associated with an increased risk of death in both the pre- (HR 2.43 [95%CI:1.24-4.76]; p=0.009) and post-chemotherapy (HR 1.85 [95%CI: 1.17-2.92]; p=0.008) settings.7 A shorter PSA doubling time has also been associated with worse outcomes in abiraterone-treated patients in the COU-AA-301 and COU-AA-302 trials.10

To our knowledge, no study has yet reported rates of primary PSA progression, or analysed the significance of an exclusive PSA progression (without radiographic) COU-AA-301 and COU-AA-302 trials. Specific data on the natural history of patients experiencing PSA-only progression are also lacking.

We aim to determine:
(a) The incidence, prognostic significance and factors associated with a PSA-only progression, either primary (at 12 weeks after treatment initiation) or secondary (after PSA response, or a lack of progression at 12 weeks) in mCRPC patients treated with abiraterone + prednisone or placebo + prednisone.
(b) Time elapsed between PSA progression and clinical/radiographic progression in mCRPC patients treated with abiraterone + prednisone or placebo + prednisone. Clinical factors associated with time between PSA progression and radiographic/clinical progression.

We anticipate our results will help clinicians perform better informed decision-making in patients with PSA progression on abiraterone, by enabling clinicians to identify patients at a high risk of clinical or radiographic progression, that may benefit from a switch of treatment to a different treatment agent before clinical deterioration ensues.

**Specific Aims of the Project:**

OVERALL AIMS:
To determine:
(1) Incidence, prognostic significance and factors associated with a PSA progression in abiraterone + prednisone and placebo + prednisone treated patients with mCRPC.
(2) Value of PSA-only progression in mCRPC abiraterone-treated patients.

SPECIFIC ENDPOINTS:
Primary Endpoint:
- Association between PSA progression and overall survival.

Secondary Endpoints:
- To evaluate, for each of the PSA progression categories (primary PSA progression, secondary PSA progression, PSA only progression):
• Incidence
• Association with OS, rPFS, cPFS, time to QoL deterioration
• Association with baseline clinical factors.
- Additionally, to evaluate for PSA only progression:
• Time to radiographic/clinical progression or death
• Time to quality of life / patient reported outcome (FACT-P) deterioration
• Baseline clinical factors associated with OS, rPFS, cPFS in patients with PSA-only progression

Exploratory Endpoints:
- To determine the rate of PSA-flare (PSA progression at 12 weeks, with a subsequent PSA response).
- To determine the rate of patients experiencing radiographic or clinical progression without a PSA progression.
- To explore Prentice Criteria for surrogacy for PSA progression.

**What is the purpose of the analysis being proposed? Please select all that apply.**
Research on clinical prediction or risk prediction

## Research Methods

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

Data Source: COU-AA-301 and COU-AA-302 datasets.

Inclusion Criteria:
Patients treated with abiraterone + prednisone or placebo + prednisone in the COU-AA-301 and COU-AA-302 trials.
Survival >= 12 weeks.
Baseline PSA value and at least one post-treatment PSA value available.

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

MAIN OUTCOME MEASURE
Overall survival, defined as the time (months) from PSA progression to death.

SECONDARY OUTCOME MEASURES
- Radiographic progression-free survival (rPFS), which will be defined as the time from PSA progression to radiographic progression or death
- Clinical progression-free survival (cPFS) or death, which will be defined as the time from PSA progression to clinical progression, in months.
- Time to quality of life deterioration will be defined as the time from PSA progression to clinically significant FACT-P or BPI-SF progression.

Radiographic and clinical progression will be defined according to the definitions established in each of the corresponding trial protocols (COU-AA-301, COU-AA-302).2,3

Quality of Life / Patient Reported Outcomes: quality of life will be quantified according to BPI-SF and FACT-P questionnaire results. Thresholds for clinically significant BPI-SF progression and/or FACT-P progression will be defined per criteria from the COU-AA-302 trial.11

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

PSA progression will be defined as a ?25% and ? 2 ng/mL increase from baseline (if no initial PSA decline is observed), or a ?25% and ? 2 ng/mL increase above the nadir (if an initial PSA decline is observed), confirmed by a second value ? 3 weeks later. Time to PSA progression will be defined as the time from treatment initiation to PSA progression.

Three categories for PSA progression will be defined:
- Primary PSA progression: PSA progression at 12 weeks
- Secondary PSA progression: PSA progression after a previous response or stable PSA at 12 weeks
- PSA-only progression (primary/secondary): PSA progression with no documented radiographic or clinical progression

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

Baseline variables:
- Treatment arm: categorical
- Ethnicity: categorical
- Age, height, weight: continuous
- Type of disease progression at baseline: categorical
- Time from LHRH treatment to trial treatment initiation
- Presence of bone, node, liver, other visceral metastases: yes/no
- Gleason Score: ordinal
- Prior surgery or radiation therapy to primary: yes/no

Baseline and at post-baseline time-points:
- Hemoglobin, albumin, alkaline phosphatase, LDH, PSA: continuous.
- ECOG PS: ordinal (0-4)

- BPI-SF score, analgesic score (continuous)
- FACT-P score (continuous)
- Post-baseline radiographic evaluation (BS/CT scan): categorical

**Statistical Analysis Plan:**

- A descriptive analysis of endpoints and baseline covariates will be performed. Results will be presented as the median and interquartile range (IQR) for continuous variables and as number and percentage frequency for categorical variables.
- Logistic regression models will be used to determine the association between PSA progression and the different baseline variables. Odds ratio estimates and 95% confidence intervals will be calculated.
- The Kaplan-Meier method will be used to estimate median survival times (OS, rPFS, cPFS) and 95% confidence intervals, in months.
- Cox proportional-hazards (Cox-PH) models will be used to test the association of PSA progression with overall survival, progression-free survival and clinical progression-free survival. Other covariates that show a significant ($p<0.05$) association with survival in the univariable Cox-PH model will be included in the multivariable Cox-PH model. If a skewed distribution is observed in any of the continuous variables, logarithmic transformation may be performed. Tests of proportionality based on Schoenefeld residuals will be applied to test the proportional hazards assumption.
- The performance of the multivariable cox-PH survival models will be evaluated by calculating Uno's inverse-probability weighted c-index and time-dependent incident dynamic ROC AUC curve values (established around the median survival of the dataset).

The COU-AA-301 dataset will be used as a test set, and the COU-AA-302 dataset will be used as a validation dataset. All analyses will be performed in the intent-to-treat populations initially, and separately in each of the trial study arms.

**Project Timeline:**

- Project submission: August 2018
- Contract: September 2018
- Analysis: September - November 2018
- Abstract Submission (ASCO GU 2019): October 2018
- Paper Draft circulation: January-February 2019
- Paper Submission: April-May 2019

**Dissemination Plan:**

- Abstract presentation in ASCO GU 2019
- Submission of manuscript first-quartile oncology journals: Annals of Oncology, European Urology, Clinical Cancer Research

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