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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/coi_yoda_rl.pdf
https://yoda.yale.edu/system/files/coi_yoda_ec.pdf
https://yoda.yale.edu/system/files/coi_david_lorente.pdf
https://yoda.yale.edu/system/files/coi_davidolmos.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

Association of Quality of Life Measures with Outcome in Metastatic Castration-resistant Prostate Cancer

Narrative Summary:

There is growing interest in the impact that treatments have on the quality of life (QoL) of advanced prostate cancer patients. QoL, measured through the FACT-P or BPI-SF questionnaires, has been consistently improved in recently reported trials. In enzalutamide-treated patients, a prognostic value of baseline FACT-P scores has been shown, highlighting its clinical significance. We aim to evaluate the association of baseline QoL with survival in abiraterone-treated patients, and to evaluate if the efficacy of abiraterone over placebo is equivalent in patients with different baseline QoL scores. We envision this may help the design of trials with specific QoL endpoints in the future.

Scientific Abstract:

Background: improvement and preservation of quality of life (HRQoL) is an important goal in advanced prostate cancer treatment. FACT-P and BPI-SF are the most frequent patient reported outcomes (PROs) used in clinical trials. In both COU-AA-301 and COU-AA-302 trials, abiraterone improved QoL and delayed the time to QoL deterioration. However, the prognostic and predictive value of QoL PROs has not been studied in patients treated with novel hormonal agents.
Objective: to evaluate the prognostic and predictive impact of HRQoL PROs in advanced prostate cancer patients treated with abiraterone or placebo.
Study Design: retrospective cohort study.
Participants: mCRPC patients treated in the COU-AA-301 and COU-AA-302 trials, with PRO (FACT-P and/or BPI-SF) data.
Main Outcome Measures: Overall survival (OS), progression-free survival (PFS).
Statistical Analysis: The association of baseline PRO scores (FACT-P, BPI-SF) with other baseline known prognostic factors will be evaluated through linear o logistic regression models. We will evaluate the association of baseline PROs, as well as changes in PRO scores after treatment initiation with OS/PFS will be evaluated with uni- and multivariable (MV) Cox Proportional Hazards (PH) models. The prognostic value of each of the FACT-P subscales will be determined by calculating the c-indices. The predictive value will be evaluated through an interaction test between treatment arm and baseline HRQoL (high vs low). Known prognostic clinical factors will be included as covariates in each of the Cox-PH models.

Brief Project Background and Statement of Project Significance:

Metastatic castration-resistant prostate cancer is a deadly disease. Despite recent advances in the systemic treatment of the disease, prolongation of survival and palliation of symptoms are still the main goals of therapy. There has been an increased interest in the impact of novel agents on the quality of life (HRQoL) of prostate cancer patients, with specific reports of the impact on HRQoL for most of the recently reported phase III clinical

trials.1–5

HRQoL is measured through patient reported outcomes (PROs). The most frequently used PROs in prostate cancer are the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the Brief Pain Inventory Short Form (BPI-SF). Additionally, fatigue has also been specifically assessed in the COU-AA-301 trial through the Brief Fatigue Inventory (BFI).

Abiraterone acetate has shown a significant benefit in overall survival in two large randomized trials in mCRPC, both of which included HRQoL outcomes as secondary objectives. COU-AA-301 patients had overall worse baseline quality of life (median BPI-SF of 3, mean baseline FACT-P 108) compared to COU-AA-302 participants (mean FACTP of 122, 65-69% of patients with BPI-SF score 0-1).6 Despite these differences, a consistent improvement of quality of life of abiraterone over placebo has been reported in all analysed endpoints of both trials. In COU-AA-301, abiraterone conferred an improved rate of pain palliation (44 vs. 27%; P = 0.002),7 faster time to palliation (5.6 vs. 13.7 mos; p = 0.0018) and more durable pain palliation (4.2 vs. 2.1 mos; p = 0.0056) as well as improved fatigue8 and FACT-P score improvement compared to placebo.9 In the COU-AA-302, abiraterone significantly improved the median time to a decline in the FACT-P score,10 as well as a median time to total HRQoL deterioration score.6

Data on the clinical significance of HRQoL measures in patients treated with abiraterone is scarce. On the other hand, in patients treated with docetaxel in the TAX-327 trial, an association of baseline pain with a significantly worse overall survival has been reported. A decrease in pain with treatment, but not an increase in QoL, was independently associated with survival.11 Similarly, data reported with enzalutamide on the AFFIRM and PREVAIL trials showed a significant association between baseline FACT-P scores and an increased survival, as well as significantly improved survival in patients that experienced a 10-point increase in FACT-P scores after starting on treatment.12

We aim to:
(a) Validate the association between QoL and survival previously reported in docetaxel and enzalutamide-treated patients
(b) Evaluate whether the benefit of abiraterone over placebo is different in patients with baseline good vs worsened quality of life.
(c) To compare the prognostic value of each of the specific QoL scales.

We anticipate our results will contribute to the growing body of evidence that emphasizes the prognostic value of baseline QoL measures, which may lead potentially to stratification by baseline QoL in clinical trials in the future and to the design of specific clinical trials addressing validated QoL endpoints.

Specific Aims of the Project:

Overall Aims:
To determine :
- Association between baseline HRQoL and outcome in metastatic castration-resistant prostate cancer treated with abiraterone.
- Value of changes in HRQoL in metastatic castration-resistant prostate cancer after treatment with abiraterone and their association with outcome.

Specific Endpoints:

Primary Endpoint:
- Association of baseline FACT-P and BPI-SF scores and overall survival.
- Association of a decline in FACT-P and BPI-SF scores and overall survival.

Secondary Endpoints:
- Association of baseline FACT-P and BPI-SF scores with:
o Radiographic, PSA, clinical progression-free survival (rPFS, PSA-PFS, cPFS).
o Other baseline prognostic clinical variables.
o Treatment-related adverse events, skeletal-related events.
- Association of %changes in FACT-P and BPI-SF scores with PSA or RECIST response.

Exploratory Endpoints:
- To evaluate the efficacy of abiraterone over placebo in patients with high vs low baseline FACT-P or BPI-SF scores.
- Correlation between time to FACT-P and BPI-SF deterioration and PSA-PFS, rPFS and OS.
- Patterns of progression (PSA, Rx, clinical) in patients with high vs low baseline FACT-P or BPI-SF scores.
- To evaluate alternative cut-off points for QoL and pain response/progression.

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 populationsConfirm or validate previously conducted research on treatment effectivenessResearch 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 PRO (FACT-P, BPI-SF or BFI) data available.

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

Main Outcome Measure
- Overall survival will be defined as the time from treatment initiation to death.

Secondary Outcome Measures
- Radiographic PFS: time from treatment initiation to radiographic progression or death.
- PSA PFS: time from treatment initiation to PSA progression or death.
- Clinical PFS: time from treatment initiation to clinical progression or death.
- PSA response: 30% decline in PSA from baseline at 12 weeks from treatment initiation, and at any time-point.
- Radiographic response: response as defined by RECIST criteria,13 only for patients with measurable disease at baseline.

Radiographic PFS, PSA-PFS and clinical PFS will be defined as per definitions on the COU-AA-301 and COU-AA-302 trials (Prostate Cancer Working Group 2 criteria).14

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

The FACT-P questionnaire comprises a general function status scale and a prostate cancer-specific (PCS) subscale, ranging from 0 to 156 (higher scores indicating better QoL).15 The BPI-SF measures individual items on a scale of 0–10, with lower scores representing lower levels of pain intensity or less interference of pain with activities of daily living.16

FACT-P and BPI-SF scores will be assessed as continuous variables, and as categorical variables, with “high” (good QoL) defined as values above the median, and “low” (worse QoL) values represented as values below the median in each of the datasets. Alternative cut-off points will also be assessed (exploratory endpoints)

A post-treatment “improvement” in FACT-P (QoL “response”) scores will be defined as an increase in 10 points from baseline scores. An increase in BPI-SF will be defined as a “pain” response. Alternative cut-off points will be assessed (exploratory endpoints).

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)
- Post-baseline radiographic evaluation (BS/CT scan): categorical
- Treatment related adverse events (graded according to CTCAE)

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.
- The Kaplan-Meier method will be used to estimate median survival times (OS, rPFS, cPFS) and 95% confidence intervals, in months.
- Linear regression models will be used to determine the association between baseline PRO scores (FACT-P, BPI-SF) when determined as a continuous variable with other baseline categorial prognostic factors.
- Logistic regression models will be used to determine the association between baseline PRO scores (FACT-P, BPI-SF) when defined as a categorical (“high” vs “low”) with other baseline categorial prognostic factors. Odds ratio estimates and 95% confidence intervals will be calculated.
- Cox proportional-hazards (Cox-PH) models will be used to test the association of baseline PROs (FACT-P, BPI-SF) as well as post-treatment changes in PROs with overall survival and progression-free survival (radiographic, PSA 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 prognostic value (association with OS) of each of the FACT-P subscales will be determined by calculating specific Cox-PH models for each of the subscales.
- The performance of each of the) of each of the Cox-PH models will be compared 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 potential predictive value of baseline QoL PRO scores will be evaluating the interaction between treatment arm (abiraterone + prednisone or placebo + prednisone) and HRQoL (“high” or “low” score) by calculating the significance of the interaction factor in a Cox-PH model.

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: November 2018
- Contract: December 2018
- Analysis: January - March 2019
- Abstract Submission (ASCO 2019): February 2019 - Paper Draft circulation: June-July 2019
- Paper Submission: August 2019

Dissemination Plan:

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

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