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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

https://yoda.yale.edu/system/files/coi_atv_for_yoda.pdf
https://yoda.yale.edu/system/files/coi_ec_for_yoda.pdf
https://yoda.yale.edu/system/files/coi_goujon_25.02.pdf
https://yoda.yale.edu/system/files/coi_anota_25.02.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

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 Health Related Quality of Life variations with biological biomarkers for patients with metastatic castrate resistant prostate cancer

Narrative Summary:

There is a paucity of data exploring association of Health Related Quality of Life (HRQOL) variations with other biological parameters that can reflect the drug toxicity or cancer bulk. Our project will use the data available from the 2 registration phase 3 trials: COUAA301 and COUAA302. These 2 trials are complementary because they have a close trial design comparing abiraterone/prednisone vs placebo/prednisone but in 2 different settings in pre or post chemotherapy. It will explore the HRQOL variations with biological biomarkers for patients with metastatic castrate resistant prostate cancer treated by abiraterone/prednisone combination or prednisone

Scientific Abstract:

Background
A potential link between PROs (patients' reported outcomes) and oncologic outcomes (progression-free survival) has been underlined in post hoc analyses of the pivotal studies for abiraterone and enzalutamide. It has been shown that patients treated with chemotherapy who experience a quality of life (QOL) improvement are also well responding with other criteria: PSA (prostate specific antigen), imaging. This type of association between biomarkers and PROs has not been explored extensively with other biological parameters that can reflect the drug toxicity or cancer bulk.
Objective
Having data showing an association between the evolution of both QOL and biological biomarkers has not yet been shown with abiraterone or other drugs
Study Design
QUA-lify study will use data from the 2 trials: COUAA301 and COUAA302.
PROs and Biological markers of interest have been collected at the baseline and throughout both trials
Participants
All patients with mCRPC treated within COUAA301 and COUAA302 with data available through YODA project will be included.
Main Outcome Measure
The primary objective is to estimate the association between improvement or deterioration in QOL and the variations of 2 strong biomarkers linked to cancer.
Statistics
Association between baseline PRO and biomarkers will be explored using correlation analysis. Patients will be classified according to their best PRO response (improvement, stability or deterioration) according to QOL's thresholds. These QOL responses will be compared with biomarkers values according to biomarkers' evolution

Brief Project Background and Statement of Project Significance:

Patients with metastatic prostate cancer (PCa) may suffer various types of symptoms, including, but not limited to, bone pain and fatigue, which can impede a patient's functional, social and emotional well-being. The patient is the primary recipient of anti-cancer treatments and there is a need to recognize and value the patient's perception in response to treatment. Assessing patient-reported outcomes , including health-related quality of life (HRQoL), using self-reported questionnaires has become an important part of clinical trials and is becoming a standard part of clinical practice. HRQoL measures enable the assessment of a patient's physical, psychological and social well-being. It can reflect cancer or treatments consequences on the patient as well as other comorbidities.

Evaluation of the response for patients with PCa is more tricky than in other tumor types due to fact that a majority of patients may have RECIST non measurable disease : lots of patients can have only bone metastases, for which classical imaging can be inconclusive. That explains why consensus was decided to have agreements on certain type of criteria clarifying the concept of progression as defined with PCWG3 (Prostate Cancer Working Group 3) recommendations.

PCa has also the particularity of having a biological marker used in the follow up of patients: PSA (prostate specific antigen). In some cases, It can be used as a trigger to initiate or change systemic therapies such as in M0CRPC (castrate resistant prostate cancer without metastasis) setting. There are published data showing that other biological parameters might be useful as prognostic biomarkers: e.g. CTCs (ciculating tumor cells), Alkaline Phosphatases.

Biological marker used in follow-up for patients with PCa may be categorized :
--biomarker more linked to cancer and its consequences: CTCs, PSA, Alkaline Phosphatases, LDH
--biomarker that can be linked to the cancer or treatment safety or other comorbidities: kalemia, glycemia, creatinine, aspartate aminotransferase, alanine aminotransferase, haemoglobin, platelet count, neutrophil count, white blood cell.
This categorization is also influenced by the stage and extent of the disease and by the type anti-cancer treatment.

A potential link between PRO and oncologic outcomes has been underlined in post hoc analyses of the pivotal studies for abiraterone and enzalutamide. PRO improvements (eg, pain, functional well-being, and physical well-being) with abiraterone or enzalutamide were significantly associated with classical endpoints such as longer overall survival and radiographic progression-free survival.

It has been shown that the patients treated with chemotherapy (docetaxel/cabazitaxel) who experience a HRQoL improvement are the ones who are well responding with other criteria : PSA, RECIST (Response Evaluation Criteria in Solid Tumours). It has not been shown extensively with other biological parameters that can reflect the drug toxicity or cancer bulk.

Having top line data showing an association between the evolution of both HRQoL and biological biomarkers has not yet been shown with abiraterone or other drugs.

Specific Aims of the Project:

The pdf synopsis attached with this submission contain more advanced and detailed sections explaining this study.

QUA-lify study will use the data available from the 2 registration phase 3 trials: COUAA301 and COUAA302. These 2 trials are complimentary because they have a close trial design comparing abiraterone/prednisone vs placebo/prednisone but in 2 different settings in pre or post chemotherapy. This is very interesting from a research perspective due to the different types of patients that were enrolled within these trials: as an example mean baseline health-related quality of life (HRQoL) assessed with FACT-P total score is lower in COUAA301 vs COUAA302 with 108 and 122 respectively. FACT-P stands for the questionnaire "Functional Assessment of Cancer Therapy - Prostate Cancer".

HRQoL questionnaires and Biological markers of interest (e.g. CTCs, PSA, Alkaline Phosphatases, Hemoglobin, LDH...) have been collected at the baseline and throughout both trials.

The primary objective is to estimate the association between improvement or deterioration in HRQOL and the variations of 2 strong biomarkers (CTCs, PSA) linked to cancer.

Other analyses that will be conducted are described in next sections

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
New research question to examine treatment safety
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:

All cases of patients with mCRPC treated within COUAA301 and COUAA302 with data available through YODA project will be included.
It is expected to get data from a total of 2283 patients with 1195 for COUAA301 and 1088 for COUAA302

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

- Definition of primary endpoint.
health-related quality of life (HRQoL) will be assessed with FACT-P total score. The 2 strong biomarkers linked to cancer will be CTCs and PSA. We will explore potential association between:
-HRQoL improvement and best responses seen on CTCs and/or PSA
-HRQoL deterioration and progressions seen on CTCs and/or PSA

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

--To qualify deterioration/improvement of HRQoL, the minimal clinically important difference is fixed to 10 points for the FACT-P total score
--For CTC reporting: baseline CTC count, will be reported as favorable or unfavorable (< 5 versus > or = 5 CTC/7.5 mL of blood, respectively. If unfavourable at the baseline, CTC will be assessed for changes after treatment : CTC conversion is defined as the change from unfavorable (five or more cells per 7.5 mL of blood) to favorable (four or fewer cells per 7.5 mL) and separately, the percent change from baseline.
--For PSA reporting: PSA response rate will be defined as the proportion of patients achieving a PSA decline > or = 50%. Definition of PSA progression : (1) after decline from baseline: record time from start of therapy to first PSA increase that is > or = 25% and > or = 2 ng/mL above the nadir, and which is confirmed by a second value > or = 3 weeks later (ie, a confirmed rising trend); (2) if no decline from baseline: PSA progression > or = 25% increase and > or = 2 ng/mL increase from baseline beyond 12 weeks.

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

Secondary objectives are to estimate
-association between improvement or deterioration in HRQOL (FACT-P subscales) and the variations of 2 strong biomarkers (CTCs, PSA) linked to cancer.
-association between improvement or deterioration in HRQOL (FACT-P TS and subscales) and the variations of less specific cancer linked biomarkers (LDH, Alkaline Phosphatases)
-association between improvement or deterioration in HRQOL (FACT-P TS and subscales) and the variations of biomarkers that can be linked to the cancer or treatment safety or other comorbidities (Hemoglobin, Albumin, Alanine aminotransferase, Aspartate aminotransferase, kalemia, glycemia, creatinine, neutrophil to lymphocyte ratio)
-association between baseline value of strong biomarkers (CTCs, PSA) linked to cancer and baseline HRQL (FACT-P TS and subscales)
-association between early variation (at 3 months) of strong biomarkers (CTCs, PSA) linked to cancer and time to HRQL (FACT-P TS and subscales) deterioration
-association between baseline value of less specific cancer linked biomarkers (LDH, Alkaline Phosphatases) and baseline HRQL (FACT-P TS and subscales)

remaining secondaries defined in the synopsis attached

Statistical Analysis Plan:

- All analysis will be performed under RStudio software. Population of analysis will be patients who have one evaluable baseline HRQOL questionnaire and at least one evaluable post-treatment initiation HRQOL questionnaire.
- All tests will be two-sided and performed at the statistical significant level of 5%.
Quantitative variables will be described using mean and standard deviation or median with interquartile and range. Qualitative variable will be described using numbers and percentages. Missing data will not be included in the percentages.

- Scores of HRQoL questionnaires will be computed according to the recommendations and described at baseline and each follow-up with the FACT-P total score, each subscale scores (physical, emotional, functional, social/family well-being), FACT-G total score, TOI (composite of the scores of physical well-being + functional well-being + prostate cancer subscale) and the prostate cancer subscale. FACT-G stands for the questionnaire “Functional Assessment of Cancer Therapy – General”.

In order to qualify the deterioration/improvement of HRQoL over time, the minimal clinically important difference (MCID) will be fixed to 4 points for each well-being subscale, 10 points for the FACT-P total score, 9 points for the FACT-G scale, 3 points for the prostate cancer subscale and 9 points for the trial outcome index [Cella Value in Health 2009; Cella Annals Oncol 2018]

- Association between baseline value of HRQoL and biomarkers will be explored using correlation analysis.
Patients will be classified according to their best HRQoL response (improvement, stability or deterioration) according to HRQoL’s thresholds detailed previously. These HRQoL responses will be compared with biomarkers values according to biomarkers’ thresholds detailed in later paragraphs.
The time to definitive HRQoL deterioration is will be defined as the time interval from the date of randomization to the date of the first clinically meaningful deterioration as compared to the baseline score, with no further clinically meaningful improvement as compared to the baseline score (Anota QoL research 2015). In the absence of confirmation of deterioration, survival time will be censored at the time of the last available HRQoL questionnaire.
The time to sustained HRQoL improvement will be also explored and defined according to recommendations (Cottone QoL research 2017).
Time to deterioration/improvement will be estimated according to Kaplan-Meier estimation method and described using median with 95% confidence interval.
Association between change in HRQoL and change in biomarkers will be assessed considering time to HRQoL deterioration/improvement as a time dependent variable in a Cox regression model for time to change in biomarkers (progression or best responses).
The association of baseline HRQoL scores with time to change in biomarkers will be also assessed.

Cox regression models will be explored. Univariate analysis will be done to explore association with time to change in biomarkers. Variables with a univariate p-value < 0.20 will be eligible for the multivariate model. Collinearity between eligible variables will be tested. Peduzzi rules of 1 variable per 10 events will be respected. Time to dependent variables could be also introduced in the model.

- Biomarkers variables and their evolution will be classified using mean and standard deviation or median with interquartile and range and recommended threshold according to literature or CTCAE (Common Terminology Criteria for Adverse Event). Some are detailed in prior section of this submission document, others are detailed within synopsis attached.
Software Used:
RStudio
Project Timeline:

The study is planned to start Q1 2020. It is estimated that it will take 2 months to check the data obtained and perform first batch of statistics to insure that data obtained are sufficient to perform the full analysis. The full statistical analysis will take 3 months after the first batch. The First draft of study report could be available for review around 6 to 8 months after the start of the study (Summer 2020).

Dissemination Plan:

-An abstract could be presented in ASCO GU 2020 congress.
-A manuscript will be concomitantly submitted to an international journal involved in Medical Oncology and/or Uro-Oncology: Annals of Oncology, European Urology, JAMA Oncology, JCO would be initial targeted journals.

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----5 Key References of the Team on that Topic from clinical perspective

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----Statistical skills of the team : 5 key references

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_training_completed_for_pi.pdf
https://yoda.yale.edu/sites/default/files/qua-lify_synopsis_yoda_project_24.03.2020.pdf
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