**Name of the project.**
QUA-lify

**Study Title.**
Association of Health Related Quality of Life (HRQOL) variations with biological biomarkers for patients with metastatic castrate resistant prostate cancer (mCRPC) treated by abiraterone/prednisone combination or prednisone.

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**Key Words**
Prostate Cancer – Health related Quality of Life – Patient-Reported Outcomes – Abiraterone – CTC – Biomarker
List of abbreviations and definitions of terms

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AUC</td>
<td>Area under the ROC curve</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CS</td>
<td>CorticoSteroids</td>
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<td>CTCs</td>
<td>Circulating Tumour Cells</td>
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<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Event</td>
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<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>eCRF</td>
<td>(electronic case report forms)</td>
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<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
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<tr>
<td>FACT-P</td>
<td>Functional Assessment of Cancer Therapy - Prostate Cancer</td>
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<td>FACT-G</td>
<td>Functional Assessment of Cancer Therapy - General</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>HRQOL</td>
<td>Health Related Quality of Life</td>
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<tr>
<td>LDH</td>
<td>Lactate DeHydrogenase</td>
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<td>LHRH</td>
<td>Luteinising hormone-Releasing hormone</td>
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<tr>
<td>LLN</td>
<td>Lower Limit of Normal</td>
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<tr>
<td>mCRPC</td>
<td>metastatic Castrate Resistant Prostate Cancer</td>
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<tr>
<td>MCID</td>
<td>Minimal Clinically Important Difference</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NHA</td>
<td>New Hormonal Agent comprising abiraterone and enzalutamide</td>
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<tr>
<td>NLR</td>
<td>Neutrophil to Lymphocyte Ratio</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>ORR</td>
<td>Objective Response Rate</td>
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<td>OS</td>
<td>Overall survival</td>
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<td>PARP</td>
<td>Poly ADP Ribose Polymerase</td>
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<td>PCa</td>
<td>Prostate Cancer</td>
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<td>PCWG</td>
<td>Prostate Cancer Working Group</td>
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<td>PD</td>
<td>Progressive Disease</td>
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<td>PK</td>
<td>pharmacokinetics</td>
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<td>PFS</td>
<td>Progression Free Survival</td>
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<td>rPFS</td>
<td>radiological Progression Free Survival</td>
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<td>PSA</td>
<td>Prostate Specific Antigen</td>
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<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumours</td>
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<td>TFSST</td>
<td>Time to First Subsequent Systemic Therapy</td>
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<td>ULN</td>
<td>Upper Limit of Normal</td>
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1. Background and Rationale

- Patients with metastatic prostate cancer 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 [1]. 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 (PROs), 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 [2]. 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.

- As displayed on figure 1, HRQOL seems to be highly correlated with the stage of the cancer with better score when the bulk of disease is low.

Figure 1. Baseline Health Related Quality of Life for 8 registration phase 3 trials in patients with castrate resistant prostate cancer in various setting (the lower on the table the more advanced is the disease). The purple rectangle highlights the FACT-P total score
● Evaluation of the response for patients with prostate cancer is more tricky than in other tumor types due to fact that a **majority of patients may have RECIST (Response Evaluation Criteria in Solid Tumours) 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 [3]. Moreover, PCWG3 also introduced the concept of “no longer clinically benefiting” (NLCB) reporting metric defined as the date and the specific reason(s) a therapy was ultimately discontinued. This allows individualized provider-patient decisions to continue or discontinue a treatment based on the primary therapeutic objective for which it is being administered and assessed, be it quality of life, PROs, or survival.

● Prostate cancer has also the particularity of having a biological marker used in the follow up of patients: PSA. 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 [4,5]. There are published data showing that other biological parameters might be useful as prognostic biomarkers: e.g. CTCs (circulating tumor cells), Alkaline Phosphatases [6-8].

● Biological marker used in follow-up for patients with prostate cancer may be categorized:
  ---biomarker more linked to cancer and its consequences: CTCs, PSA, Alkaline Phosphatases, LDH (lactate dehydrogenase)
  ---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 of 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 (e.g., 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 [9,10].
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 [11]. 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.

References


2. Study Description

QUA-ify study will use the data available from the two 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. 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 HRQOL assessed with FACT-P total score used in both trials is lower in COUAA301 vs COUAA302 with a mean score of 108 vs. 122 respectively (table 1).

HRQOL questionnaires and other PROs have been collected at the baseline and throughout both trials. Biological markers of interest (e.g. CTCs, PSA, Alkaline Phosphatases, Hemoglobin, LDH) have also been collected at the baseline and throughout both trials. Timelines for HRQOL questionnaires and biological markers’ collection were not identical in both trials: analyses will be performed separately for each trial and whenever possible with both trial data pooled together.

Endpoints and analyses that will be conducted are described in next sections.

2.1. Study Objectives

● The primary objective is to estimate the association between improvement or deterioration in HRQOL (FACT-P Total score (TS)) and the variations of 2 strong biomarkers (CTCs and PSA) linked to cancer. FACT-P stands for the questionnaire “Functional Assessment of Cancer Therapy - Prostate Cancer”.

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

2.2. Study Endpoints

- **Definition of primary endpoint.**
  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

- **Definition of secondary endpoint.**
  HRQoL will be assessed with (FACT-P subscales). 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

HRQoL will be assessed with FACT-P total score and subscales. Less specific biomarkers linked to cancer will be LDH, Alkaline Phosphatases. We will explore potential association between:
--HRQoL improvement and best responses seen on LDH and/or Alkaline Phosphatases
--HRQoL deterioration and progressions seen on LDH and/or Alkaline Phosphatases
HRQoL will be assessed with FACT-P total score and subscales. Biomarkers that can be linked to the cancer or treatment safety or other comorbidities will be: hemoglobin, albumin,alanine aminotransferase, aspartate aminotransferase, kalemia, glycemia, creatinine, neutrophil to lymphocyte ratio. We will explore potential association between:
- HRQoL improvement and improvements seen on these biomarkers
- HRQoL deterioration and deterioration seen on these biomarkers.

Baseline HRQoL will be assessed with FACT-P TS and subscales. The 2 strong biomarkers linked to cancer will be CTCs and PSA. We will explore potential association between higher or lower HRQoL scores and these biomarker value at the baseline.

HRQoL will be assessed with FACT-P TS and subscales. The 2 strong biomarkers linked to cancer will be CTCs and PSA. We will explore potential association between early variation (response or progression at 3 months) of these biomarkers and the time to HRQoL (FACT-P TS and subscales) deterioration.
--The time to HRQoL deterioration will be defined as the time interval from the date of randomization to the date of the first definitive deterioration (below 10 points for FACT-P TS, other thresholds for subscales detailed in statistical section). In the absence of confirmation of deterioration, survival time will be censored at the time of the last available HRQoL questionnaire.
--The time to HRQoL improvement will be defined as the time interval from the date of randomization to the date of the first sustained improvement (above 10 points for FACT-P TS, other thresholds for subscales detailed in statistical section). In the absence of confirmation of improvement, survival time will be censored at the time of the last available HRQoL questionnaire.

Baseline HRQoL will be assessed with FACT-P TS and subscales. The less specific cancer linked biomarkers will be LDH, Alkaline Phosphatases. We will explore potential association between higher or lower HRQoL scores and these biomarker values at the baseline.

HRQoL will be assessed with FACT-P TS and subscales. The less specific cancer linked biomarkers will be LDH, Alkaline Phosphatases. We will explore potential association between early variation (response or progression at 3 months) of these biomarkers and the time to HRQL (FACT-P TS and subscales) deterioration/improvement. The time to HRQoL deterioration/improvement has been defined above.
Baseline HRQoL will be assessed with FACT-P TS and subscales. The biomarkers that can be linked to the cancer or treatment safety and other comorbidities will be Hemoglobin, Albumin, Alanine aminotransferase, Aspartate aminotransferase, Potassium, neutrophil to lymphocyte ratio (NLR). We will explore potential association between higher or lower HRQoL scores and these biomarker values at the baseline.

HRQoL will be assessed with FACT-P TS and subscales. The biomarkers that can be linked to the cancer or treatment safety and other comorbidities will be: Hemoglobin, Albumin, Alanine aminotransferase, Aspartate aminotransferase, Potassium, Neutrophil to Lymphocyte (NLR) ratio. We will explore potential association between early variation (improvement or deterioration at 3 months) of these biomarkers and the time to HRQL (FACT-P TS and subscales) deterioration/improvement. The time to definitive HRQoL deterioration/improvement has been defined above.

2.3. Patients Identifications and selection
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.

2.4. Data Collection
Data will be collected thanks to YODA project.

3. Statistical methods
- Population of analysis will be patients who have one evaluable baseline HRQOL questionnaire and at least one evaluable post-treatment initiation HRQOL questionnaire. We will compare the baseline patients’ characteristics of this population of analysis and all patients treated within COUAA301 and COUAA302.

- All analysis will be performed under RStudio software. 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 et al. Value in Health 2009; Cella et al. 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 [ref Anota et al. 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 [Coens et al. Lanc Oncol 2020].

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.

  --For CTC reporting: baseline CTC count, will be reported as favorable or unfavorable (< 5 versus ≥ 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 [Scher et al.JCO 2016].

  --For PSA reporting: PSA response rate will be defined as the proportion of patients achieving a PSA decline ≥ 50%. Definition of PSA progression: (1) after decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend); (2) if no decline from baseline: PSA progression ≥ 25% increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks [Scher et al.JCO 2016].

  --For biomarkers that could be linked to treatment safety (Hemoglobin, Albumin, Alanine aminotransferase, Aspartate aminotransferase, Potassium) CTCAE classification will prevail.

  --For less specific cancer linked biomarkers (LDH, Alkaline Phosphatases), we will report (1) if elevated at the baseline their decline from baseline, their normalisation or their progression. (2) if not elevated at the baseline only their progression

  --For NLR: we will report (1) if elevated at the baseline the decline from baseline to a cut-off <3 or <5, or their progression. (2) if not elevated at the baseline only their progression above a cut-off ≥ 3 or ≥5; (3) a sensitivity analysis with NLR as a continuous variable.

References:


4. Results and Outcomes

Through this collaboration with YODA project:
- 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.

6. Timetable: estimated study dates.

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 ensure 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).

10 Key Bibliographic References of the Team on that Topic.

5 from Clinical Perspective


5 from Statistical skills:


