Principal Investigator

First Name: Rebeca
Last Name: Lozano
Degree: MD
Primary Affiliation: Spanish National Cancer Research Centre (CNIO)
E-mail: rebecalozanomejorada@gmail.com
Phone number:
Address: Melchor Fernandez Almagro, 3

City: Madrid
State or Province: Madrid
Zip or Postal Code: 28029
Country: España

General Information

Key Personnel (in addition to PI):
First Name: David
Last name: Lorente
Degree: MD
Primary Affiliation: Medical Oncology Service, Hospital Provincial de Castellón
SCOPUS ID: 55944529300

First Name: David
Last name: Olmos
Degree: MD, PhD
Primary Affiliation: Spanish National Cancer Research Centre (CNIO)
SCOPUS ID:

First Name: Elena
Last name: Castro
Degree: MD, PhD
Primary Affiliation: Spanish National Cancer Research Centre (CNIO)
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

https://yoda.yale.edu/system/files/rl_yoda_project_coi_form_nomogram.pdf
https://yoda.yale.edu/system/files/coi_david_lorente_0.pdf
https://yoda.yale.edu/system/files/do_yoda_project_coi_nomogram.pdf
https://yoda.yale.edu/system/files/ec_signed_yoda_project_coi.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. 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

External validation of a prognostic nomogram for first-line therapy in metastatic castration-resistant prostate cancer

Narrative Summary:

Although several life-prolonging therapies have been developed for metastatic castration-resistant prostate cancer (mCRPC), optimal sequence is unknown. In this setting, it is necessary to develop and validate prognostic models that reflect outcomes from currently treatments. In enzalutamide-treated patients at first-line, a novel nomogram that measures overall survival has been developed, identifying subsets of patients with different survival outcomes, through well-known prognostic variables. We aim to validate the prognostic value of this nomogram in mCRPC patients receiving abiraterone as first-line treatment. This could help in stratification and patient selection in clinical trials.

Scientific Abstract:

Background: Currently, several life-prolonging therapies have been approved for metastatic castration-resistant prostate cancer (mCRPC) patients, however, evidence on the optimal sequence is lacking, and prognosis assessment remains an important issue. Recently, Armstrong et al have developed a novel prognostic nomogram for men with mCRPC treated with first-line enzalutamide. Nonetheless, the prognostic value of this model has not been analysed in mCRPC patients treated at first-line with abiraterone.

Objective: To assess the prognostic value of Armstrong nomogram for survival estimation in mCRPC patients treated in the COU-AA-302 trial.

Study Design: Retrospective cohort study

Participants: mCRPC patients treated on a prospective randomized clinical trial of abiraterone plus prednisone vs placebo plus prednisone in first-line of mCRPC (COU-AA-302)

Main Outcome Measures: Overall survival (OS), progression-free survival (PFS)

Statistical Analysis: Baseline risk scores according to the Armstrong nomogram will be calculated for each patient. Cox proportional-hazards (Cox-PH) models will be used to test the association of baseline risk scores / risk groups (low, intermediate, high) with OS and PFS. The prognostic ability of the models will be evaluated through Uno's inverse-probability weighted c-index and time-dependent ROC AUC values. The impact of treatment arm in each of the risk groups (stratified Cox-PH models) and the association with baseline quality of life measures (linear and logistic regression models) will also be evaluated.

Brief Project Background and Statement of Project Significance:

Currently, there are several options available for the treatment of metastatic Castration Resistant Prostate Cancer (mCRPC)(1-8), however, evidence on the optimal treatment sequence is lacking. Traditionally, the selection of strategies is based largely in clinical symptoms, comorbidities, expected side-effects and preferences by the

patient.

It is important to assess the prognosis before starting a new therapy, in order to counsel patients about their long-term outcomes, and to guide treatment selection.
In this setting, prognostic models are useful tools that estimate the risk for disease-related mortality(9), and can play an important role for stratification and patient selection in clinical trials.
Prognostic models and nomograms for mCRPC patients have been developed in localized disease, and those for mCRPC were developed in patients receiving first- and second-line treatment(10-14). They contain different variables including both tumour and host factors.

Recently, Armstrong et al(15) have developed a novel nomogram that provides prognostic information using data collected from the PREVAIL trial, which compared enzalutamide with placebo in first-line of mCPRC patients. The model contains 11 known prognostic variables, including albumin, alkaline phosphatase (ALP), haemoglobin, lactate dehydrogenase (LDH), prostate specific antigen (PSA), number of bone metastases, presence if pain, pattern of spread, time since diagnosis, treatment and neutrophil-to-lymphocyte ratio (NLR). This model demonstrated a significant difference in overall survival (OS) for the low-risk group (HR: 0.20; 95% CI 0.14-0.29) and intermediate-risk group (HR: 0.40; 95% CI 0.30-0.53) compared with high-risk group.
However, these findings have not been analysed in other datasets of patients with mCRPC treated at first-line with abiraterone, and further external validation is needed.

We aim to:
i) Validate the prognostic nomogram carried out by Armstrong et al using an external dataset of patients treated on a prospective randomized clinical trial of abiraterone plus prednisone vs placebo plus prednisone in first-line of mCRPC (COU-AA-302)
ii) Evaluate the association between the different prognostic risk groups (low, intermediate or high) and overall survival in patients treated with abiraterone plus prednisone

If validated, this model could allow the assessment of risk in patients with mCRPC treated at first line with novel androgen receptor signalling inhibitors (ARSI), such as abiraterone or enzalutamide, through the use of factors that are routinely assessed in clinical practice, identifying subsets of patients with different survival outcomes.

Specific Aims of the Project:

OVERALL AIMS:
To validate the prognostic value of the Armstrong nomogram15 for survival estimation in metastatic castration-resistant prostate cancer patients undergoing first-line treatment with abiraterone + prednisone or placebo + prednisone.

SPECIFIC ENDPOINTS:
Primary Endpoint:
- Association of prognostic risk groups (low, intermediate, high) with overall survival.

Secondary Endpoints:
- Association of prognostic risk groups (low, intermediate, high) with radiographic progression-free survival (rPFS).
- Association of prognostic risk groups (low, intermediate, high) with PSA progression-free survival (PSA-PFS).
- Evaluation of the prognostic ability of the nomogram score as a continuous variable.

Exploratory Endpoints:
- Impact of trial treatment (abiraterone vs placebo) on OS, rPFS and PSA-PFS in each of the prognostic risk groups.
- Evaluation of baseline quality of life (QoL) scores (FACT-P, BPI-SF), QoL response and time to QoL deterioration in each of the prognostic risk groups.
- Patterns of disease progression in each of the prognostic risk groups.

What is the purpose of the analysis being proposed? Please select all that apply.
Confirm 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-302 datasets

Inclusion Criteria:
Patients treated with abiraterone + prednisone or placebo + prednisone in the COU-AA-302 trial.
Baseline clinical variables included in Armstrong nomogram available (albumin, ALP, Hemoglobin, LDH, NLR, Number of bone metastases, Presence of pain, pattern of spread, PSA, Time from diagnosis to randomisation, Treatment)

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

Main Outcome Measure

- Overall survival will be defined as time from randomization to death.

Secondary Outcome Measures

- Radiographic progression-free survival: time from randomization to radiographic progression* or death.
- PSA progression-free survival: time from randomization to PSA progression* or death.
- Clinical progression-free survival: time from randomization to clinical progression* or death.
- QoL endpoints: High vs low quality of life scores will be defined as values above and below the median QoL score (FACT-P, BPI-SF) in each of the datasets. A QoL response will be defined as an ? 10 point increase in FACT-P scores relative to baseline. A pain response will be defined as an increase in BPI-SF scores.

*Radiographic, clinical and PSA progression will be defined as per Prostate Cancer Working Group 2 criteria (16)

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

The main predictor in our study will be the prognostic score defined by Armstrong et al, which is calculated from a number of clinical variables (see Table 1)

The score will be evaluated as a continuous variable.

Risk factors included in the prognostic nomogram will also be categorized into three risk groups. Variables defined as continuous in the nomogram (albumin, haemoglobin, PSA, TDR) will be categorized as follows:
- PSA: > 50 ng/mL
- Albumin: < 4 g/dL
- Hemoglobin: < 12.5 g/dL
- TDR: < 60 months

Three risk groups will be categorized as defined by Armstrong et al:
- High risk: 7-10 risk variables
- Intermediate risk: 4-6 risk variables
- Low risk: 0-3 risk variables

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

In addition to variables included in the risk score (see “main predictor/independent variable”), the following variables will be collected:

Baseline variables:
- Treatment arm: categorical
- Ethnicity: categorical
- Age, height, weight: continuous
- Type of disease progression at baseline: categorical
- De novo metastatic disease: yes/no
- 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
- Use of steroids at baseline

Baseline and at post-baseline time-points:
- ECOG PS: ordinal (0-4)
- Post-baseline radiographic evaluation (BS/CT scan): categorical
- Treatment related adverse events (graded according to CTCAE)
- FACT-P, and BPI-SF scores at baseline and at each post-treatment and follow-up visit
- Post-progression lines of treatment

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, time to QoL deterioration) and 95% confidence intervals, in months.
- Cox proportional-hazards (Cox-PH) models will be used to test the association of baseline risk score (continuous variable) or baseline risk groups (low, intermediate, high) with overall survival and progression-free survival (radiographic, PSA and clinical progression-free survival). Tests of proportionality based on Schoenefeld residuals will be applied to test the proportional hazards assumption.
- The prognostic ability of the prognostic scores will be evaluated by calculating Uno's inverse- probability weighted c-index and time-dependent incident dynamic ROC AUC curve values of each of the Cox-PH models.
- The impact of treatment arm (abiraterone vs placebo) will be evaluated through a stratified Cox-PH analysis (stratified by risk group: low, intermediate, high) incorporating treatment arm as a covariate. The significance of the interaction factor between treatment arm and risk score in Cox-PH models will also be determined.
- 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 the prognostic score (nomogram) when evaluated as a continuous variable. Spearman's correlation coefficients will be calculated.
- 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 Armstrong baseline risk categories ("high", "intermediate", "low"). Odds ratio estimates and 95% confidence intervals will be calculated.

Project Timeline:

- Project submission: December 2018
- Contract: January 2019
- Analysis: January-March 2019
- Abstract submission (ASCO 2019): February 2019
- Paper draft circulation: June-August 2019
- Paper submission: October-November 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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Supplementary Material:

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