Principal Investigator

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General Information

Key Personnel (in addition to PI):

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_david_lorente_1.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. NCT01715285 - 212082PCR3011 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

PSA Progression in High-Risk Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

Narrative Summary:

The assessment of treatment efficacy in mCSPC is hindered by the fact that response to primary ADT is achieved

in an overwhelming majority of patients. A number of alternative PSA response measures have been studied. The clinical significance of PSA progression is however unclear, especially in the absence of clinical/radiographic progression. Trials did not mandate treatment discontinuation based on PSA progression; its significance is, therefore, unknown.

We aim to evaluate the clinical significance of a PSA progression in patients from the LATITUDE study, as well as clinical features that may help identify patients at a high risk of clinical or radiographic progression.

Scientific Abstract:

Background: PSA progression (PSAProg) at 7 months has been associated with decreased overall survival in mCSPC patients treated with ADT in the SWOG 9346 trial. Abiraterone acetate has been shown to significantly prolong survival in combination with ADT in patients with mCSPC in the LATITUDE trial; patients on PSA progression only were allowed to continue on study. The clinical significance of PSA progression in mCSPC patients is poorly understood.

Objective: to evaluate the incidence, prognostic significance and factors associated with PSAprog in high-risk mCSPC patients.

Study Design: retrospective cohort study.

Participants: mCSPC patients treated in the LATITUDE trial, with a baseline and at least one post-treatment PSA value.

Main Outcome Measures: Overall survival.

Statistical Analysis: The proportion of patients experiencing PSAprog at pre-specified timepoints 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. 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 metastatic, castration-sensitive prostate cancer represents only 3% of new prostate cancer diagnoses in the United States,1 it is the form of presentation in approximately half of patients that ultimately die from the disease.2 Traditionally, treatment for mCSPC was based on androgen deprivation therapy through orchiectomy or GnRH analogues, with contemporary series reporting a median 11 month failure-free survival, and median overall survival of 42 months.3

In recent years, several phase III trials have reported a significant improvement in overall survival with the addition of docetaxel to ADT (GETUG-AFU-15, CHAARTED, STAMPEDE),4–6 followed by trials evaluating ADT + abiraterone (LATITUDE, STAMPEDE)7,8 and, more recently, trials evaluating apalutamide (TITAN)9 and enzalutamide (ENZAMET, ARCHES),10,11 setting new therapy standards for the disease.

The randomized, double-blind, placebo-controlled LATITUDE study compared efficacy and safety of abiraterone + prednisone + ADT with placebo + ADT in men with high-risk mCSPC, demonstrating significantly longer overall survival (OS) and radiographic progression-free survival (rPFS).7 In a recently published post-hoc analysis of the LATITUDE trial, the association of a PSA response (50% or 90% decline from baseline), rates of PSA < 0.2 ng/mL, nadir PSA, time to PSA progression and time to PSA nadir were all found to be significantly associated with radiographic progression-free survival and overall survival.7

In mCSPC, the impact of PSA progression is less-well known. In the SWOG 9346 trial, the association of PSA progression at any time and OS, and between PSA progression status at 7 months and survival was evaluated. Both PSA progression endpoints were associated with a > 4 times increase in the risk of death; median subsequent

OS was 10 months versus 44 months in patients who did or did not have PSA progression by 7 months.12

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

We aim to:
(a) Determine the incidence, prognostic significance and factors associated with a PSA-only progression, either primary (at 7 months after treatment initiation) or secondary (after PSA response, or a lack of progression at 7 months) in mCSPC patients treated with abiraterone + prednisone or placebo + prednisone.

(b) Compare the prognostic ability of PSA progression measures with other PSA response measures

(c) Determine the time elapsed between PSA progression and clinical/radiographic progression or death, as well as 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 for mCSPC, by enabling clinicians to identify patients at a high risk of clinical or radiographic progression, that may benefit from a treatment switch.

Specific Aims of the Project:

Overall Aims:
- To validate the prognostic impact of PSA progression at 7 months (PSA-P) after treatment initiation in metastatic hormone-sensitive prostate cancer.

Specific Endpoints:

Primary Endpoint:
- Association between PSA-P and overall survival

Secondary Endpoints:
- Factors associated with overall survival at the time of PSA progression.
- Association between PSA-P and radiographic progression-free survival.
- Time from PSA progression to radiographic progression
o Proportion of patients with and without visceral disease progression.
- Time from PSA progression to:
o Subsequent therapy initiation
o Pain progression
o QoL deterioration
o Skeletal-related events
- Proportion of patients with (at the time of PSA progression):
o PSA progression exclusively
o PSA + radiographic progression
o PSA + radiographic + clinical progression
- Association between PSA-P at 12, 18 and 24 months with overall survival, radiographic progression-free survival and time to QoL deterioration.

Exploratory Endpoints:
- Comparison of PSA progression with other PSA-derived endpoints (90% PSA response, 50% PSA response, PSA < 0.02 ng/mL).

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

Research Methods

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

Data Source: LATITUDE trial dataset

Inclusion Criteria:
Patients treated with ADT + abiraterone + prednisone or ADT + placebo + prednisone in the LATITUDE trial
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 the LATITUDE trial protocol.

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 LATITUDE trial protocol.

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

PSA progression will be defined according to PCWG3 guidelines 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.

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:

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- 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).

All analyses will be performed in the intent-to-treat populations initially, and separately in each of the trial study arms.
Software Used:
RStudio

Project Timeline:

- Project submission: April 2020
- Contract: April-May 2020
- Analysis: June-November 2020
- Abstract Submission (ASCO GU 2021): October 2020 - Paper Draft circulation: January-February 2021
- Paper Submission: April-May 2021

Dissemination Plan:

- Abstract presentation in ASCO GU 2021
- Submission of manuscript first-quartile oncology journals: Annals of Oncology, European Urology, Clinical Cancer Research

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