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General Information

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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/jun_wang.pdf
https://yoda.yale.edu/system/files/junliang_zhao.pdf
https://yoda.yale.edu/system/files/xinyang_cai.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

3. 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

The Impact of Dose Timing on the Efficacy and Safety of Abiraterone Acetate plus Prednisone in Men with Advanced Prostate Cancer

Narrative Summary:

A circadian rhythm exists in androgen synthesis and releasing. Administering Abiraterone at night may more effectively suppress the morning peak of androgen synthesis and release, leading to improved therapeutic effectiveness. To test this hypothesis, we hope to evaluate the survival outcomes of advanced prostate cancer patients with different dosing times (Nighttime vs. Daytime) across COU-AA-301, COU-AA-302, and LATITUDE these three clinical trials. We aim to clarify the effect of dosing time on the efficacy and safety of abiraterone. This analysis may provide evidence for establishing the optimal dosing time of abiraterone.

Scientific Abstract:

Background: Androgen deprivation therapy (ADT) is the cornerstone of the treatment of advanced prostate cancer, mainly blocking the synthesis and secretion of androgen. Levels of various hormones fluctuate throughout the day due to the circadian rhythm of the endocrine system.
Objective: To investigate the effect of dose timing on the efficacy and safety of abiraterone acetate plus prednisone in advanced prostate cancer patients.
Study Design: Post-hoc analysis of patients participating in randomized controlled trials.
Participants: Patients with advanced prostate cancer who were enrolled in COU-AA-301, COU-AA-302, and LATITUDE, with documented dosing times.
Main Outcome Measures: Progression-free survival (PFS), overall survival (OS) and prostate-specific antigen progression-free survival (PSAprog-PFS) will be determined. In addition, the adverse events (AEs) will be described based on different time groupings.
Statistical Analysis: Baseline data will be described by descriptive statistics (median ±SD), and comparison between groups will be performed by student t test or chi-square test. PFS, OS and PSAprog-PFS will be estimated by Kaplan-Meier analysis, with hazard ratios calculated using a multivariate Cox proportional-hazard model. AEs will be described by descriptive statistics (incidence rate).

Brief Project Background and Statement of Project Significance:

Palliative treatment based on androgen deprivation therapy (ADT) is the standard treatment for metastatic prostate cancer (mPCa) [1, 2]. After receiving ADT alone for about 1-2 years?mPCa will progress to metastatic castration-resistant prostate cancer (mCRPC). Drug resistance will eventually occur in the novel hormone therapy (NHT)?and the prognosis is poor. Delaying the time of drug resistance can prolong the life of patients.
Circadian rhythm refers to the rhythmic changes of life activity with a cycle of about 24 hours[3-6]. Testosterone shows a significant circadian rhythm as well. ADT is the cornerstone of the treatment of mPCa?mainly blocking the synthesis and secretion of androgen. Will the regulation of circadian rhythm on the endocrine system affect the efficacy of hormone therapy?
Testosterone levels in both normal and hypogonadal men changes day and night?whose synthesis begins at night and reaches its peak in the morning (around 10:00)?then decreases and reaches its trough at night (around 20:00) [7, 8]. Therefore?we propose whether the timing adjustment based on circadian rhythm has any effect on the

efficacy and safety of NHT (Abiraterone acetate plus prednisone) for prostate cancer?
The purpose of this study is to retrospectively compare the progression-free survival (PFS)?overall survival (OS)?prostate-specific antigen progression-free survival (PSAprog-PFS) and adverse events (AEs) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) who receive Abiraterone acetate plus prednisone during the daytime or at night to explore the effect of timing adjustment based on circadian rhythm on the efficacy and safety of NHT agents. The results are expected to provide guidance for clinical diagnosis and treatment?improve the prognosis of patients and benefit more patients with advanced prostate cancer.

Specific Aims of the Project:

Aims: Using individual patient data from COU-AA-301, COU-AA-302, and LATITUDE these three clinical trials which including advanced prostate cancer patients treated with Abiraterone to perform dosing time stratified (daytime vs. nighttime) analysis for PSAprog-PFS, PFS and OS survival.
Hypothesis: Androgen synthesis follows a circadian rhythm, with the highest synthesis and release occurring in the morning. Our hypothesis is that administering the Abiraterone at night may better suppress the morning peak of androgen release and therefore be more effective.

What is your Study Design?:

Meta-analysis (analysis of multiple trials together)

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

Summary-level data meta-analysis

Summary-level data meta-analysis using only data from YODA Project

Participant-level data meta-analysis

Summary-level data meta-analysis using only data from YODA Project

Research Methods

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

1. A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Participants With High-Risk, Metastatic Hormone-Naive Prostate Cancer (mHNPC) (NCT01715285)
2. Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer (NCT00887198)
3. Abiraterone Acetate in Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy (NCT00638690)

Inclusion criteria: all patients in the trials
Exclusion criteria: missing data of dosing times

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary end points:
- Overall survival, defined as the time (months) from registered to death.
- Radiographic progression-free survival (rPFS), which will be defined as the time from registered to radiographic progression or death.

- Clinical progression-free survival (cPFS) or death, which will be defined as the time from registered to clinical progression, in months.

Secondary end points: PSA response rate (PSA30, PSA50, and PSA90), safety.

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

Dose timing will be categorized as Nighttime dosing (20:00-08:00) and Daytime dosing group (08:00-20:00). Patients who had both dosing patterns during the treatment cycle were classified based on the pattern that accounted for more than 80% of the time.

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

Age (categorized), race, Eastern Cooperative Oncology Group (ECOG) performance status (0 or ?1), baseline prostate-specific antigen (PSA) (categorized), Gleason score at diagnosis (categorized), prior taxane (no or yes), Tumor Stage, Nodal Stage, Metastases Stage, time from diagnosis to randomization. Baseline laboratory test results (PSA, Hb, LDH, ALP, and ALB). Survival data (PSAprog-PFS, PFS and OS). PSA response rate (PSA30, PSA50, and PSA90), AEs.

Statistical Analysis Plan:

Participants who had the same treatment will be divided by Dose timing (Nighttime and Daytime). Baseline data will be described by descriptive statistics (median ±SD), and comparison between groups will be performed by student t test or chi-square test. Kaplan-Meier analysis and established multivariate Cox proportional-hazard model will be performed by survival and survminer package. AEs will be described by descriptive statistics (incidence rate).
Software Used:
STATA
Project Timeline:

We anticipated start the project In September this year, finish the analysis before 1 Oct 2024, and draft the manuscript for submission before 1 July 2024.

Dissemination Plan:

The findings of this project are expected to result in the development of a manuscript suitable for publication in a urologic (European Urology, Journal of Urology) or oncology (Annals of Oncology, JAMA oncology) journal. In addition, the results will be presented at appropriate urologic (AUA, EAU) or oncology conferences (ASCO, ESMO).

Bibliography:

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.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }