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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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/20220808coizy.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. NCT02257736 - 56021927PCR3001 - A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC)

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 long-term proton pump inhibitors use on the prognosis of patients receiving Androgen-annihilation therapy.

Narrative Summary:

Androgen-annihilation therapy (abiraterone, apalutamide, bicalutamide, SHR3680…… plus prednisone) has become the standard treatment for mHSPC/mCRPC patients. The impact of long-term PPI on the prognosis of patients receiving Androgen-annihilation therapy is still unknown. Therefore, in this study, we will focus on the difference in prognosis between patients who take PPI for a long time and those who do not take PPI drugs among patients receiving Androgen-annihilation therapy.

Scientific Abstract:

Background:
The use of proton pump inhibitors (PPI) may affect the bioavailability of drugs. However, the effect of long-term PPI use on the prognosis of patients receiving Androgen-annihilation therapy is still unknown.
Objective:
We plan to perform a pooled analysis of ACIS and CHART trial, to compare the radiographic progression-free survival (rPFS) and overall survival (OS) in patients with or without long-term PPI use.
Study Design:
Patients from ACIS and CHART treated with apalutamide + abiraterone, abiraterone, bicalutamide, SHR3680 will be classified according to the use of PPI. We will then explore whether long-term PPI use affect the prognosis of patients receiving Androgen-annihilation therapy.
Participants:
Patients receiving Androgen-annihilation therapy from ACIS and CHART. CHART (NCT03520478) is an open, multicenter, randomized phase III trial led by our center[5].
Primary and Secondary Outcome Measure(s):
Overall survival & Radiographic progression free survival
Statistical Analysis:
R Statistical software will be used for all assessments. Patients will be first classified into four groups according to the Androgen-annihilation therapy they received. Baseline data of patients in each group (PPI use or not) will be first balanced by Propensity Score Matching (PSM) and then estimated by Kaplan-Meier analysis, with hazard ratios calculated using a multivariate Cox proportional-hazard model.

Brief Project Background and Statement of Project Significance:

Prostate cancer (PCa) is the second most commonly diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide, with an estimated 1,414,259 new cancer cases and 375,304 deaths in 2020[6]. Androgen-annihilation therapy (abiraterone, apalutamide, bicalutamide, SHR3680…… plus prednisone) has become the standard treatment for mHSPC/mCRPC patients.
Proton pump inhibitors (PPI) are widely used in general population as well as patients with prostate cancer. These drugs will change the pH of gastrointestinal tract, affect the secretion and biological activity of lipase, and thus affect the bioavailability of drugs[1]. In previous studies, PPIs have been proven to affect the absorption of chemotherapy drugs and immunosuppressants, thereby improving the prognosis of patients with urothelial carcinoma[2], non-small-cell lung cancer[3], and gastroesophageal cancer[4]. However, the effect of long-term PPI on the prognosis of patients receiving Androgen-annihilation therapy is still unknown.
The clinical trial we applied for is ACIS, which includes patients treated with two common Androgen-annihilation therapy (apalutamide + abiraterone, abiraterone). Another clinical trial included in this study is CHART, that contains patients treated with bicalutamide, SHR3680. Thus, we can test our hypothesis in four different Androgen-annihilation therapies, which will greatly increase the range of patients who will benefit from our study.
Our research, whether the final result is positive or negative, will improve clinicians and patients' understanding of Androgen-annihilation therapy combined with PPI drugs. If our study shows that PPI drug use is beneficial to the prognosis of prostate cancer patients receiving Androgen-annihilation therapy, we may encourage patients to take PPI at the same time in the future treatment process. In contrast, if the outcome is negative, we may advise patients temporarily stop taking PPI when receiving Androgen-annihilation therapy. If there is no association

between long-term PPI use and the prognosis of Androgen-annihilation therapy, it will also eliminate clinicians' concern about whether to continue using PPI when patients receiving Androgen-annihilation therapy.

Specific Aims of the Project:

Objective: Using individual patient data from NCT02257736 and NCT03520478 which including patients treated with different Androgen-annihilation therapy (apalutamide + abiraterone, abiraterone, bicalutamide, SHR3680) to explore the impact of long-term PPI use on the prognosis of these patients.
Hypothesis: Patients with long-term PPI may have better prognosis after Androgen-annihilation therapy.

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

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

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:

Individual patient data from ACIS (NCT02257736) dataset and CHART (NCT03520478) dataset.
CHART (NCT03520478) is an open, multicenter, randomized phase III trial led by our center[5]. The data of CHART will be obtained from the sponsor Jiangsu HengRui Medicine Co., Ltd. after permission. The individual patient data from these two clinical trials will be analyzed respectively. We will conduct the IPD analysis of CHART in the local computer. In sum, we will conduct the IPD analysis of ACIS on YODA platform and the analysis of CHART locally.
All the patients from these two clinical trials received Androgen-annihilation therapy (apalutamide + abiraterone, abiraterone, bicalutamide, SHR3680) will be included in this post-hoc analysis. Meanwhile, patients whose baseline information or outcomes were incomplete will be excluded.

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

Primary end points include overall survival and radiographic progression-free survival in patients with or without long-term PPI after treated by Androgen-annihilation therapy.
Secondary end points include PSA response and safety.

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

PPI use (long-term: use PPI before randomization and continue in the process of treatment vs. other patients), Clinicopathological variables as age, body mass index, Gleason score, tumor stage, performance of status, site of metastases, PSA, medication, comorbidity, et al.

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

- Treatment arm: Categorical

- Race: Categorical
- Age: Continuous
- Gleason Score at initial diagnosis: Ordinal
- Prior radical prostatectomy: yes/no (categorical)
- Prior radiation therapy: yes/no (categorical)
- Date of prior radical prostatectomy and prior radiation therapy with indications
- ECOG PS: Ordinal
- Date of randomization
- Prior systemic treatment (ADT) – (categorical)
- Tumor stage at diagnosis
- Nodal stage at diagnosis
- Metastatic stage at diagnosis
- Time from initial diagnosis to randomization in years (continuous)
- Time from initiation of ADT or orchiectomy to randomization in years
- Visceral metastasis (yes or no with sites)
- No. of skeletal metastasis

Baseline and Post-Baseline Variables:
- PSA and alkaline phosphatase at time of study entry
- Post-baseline radiographic evaluation (bone scan/CT scan/MRI): categorical
- Time of radiographic, clinical, or PSA progression (date format) – to calculate time to progression
- Deaths (yes/no)
- Time of death (date format) and cause of death
- Time to cytotoxic chemotherapy
- Life prolonging therapy received after progression – (Yes/No) & details (regimen, date)

Statistical Analysis Plan:

Participants who had the same treatment will be divided by PPI use (long-term: use PPI before randomization and continue in the process of treatment vs. other patients). Propensity score methods (PSM) will be used to balance the baseline differences among different races. PSM will be performed by MatchIt package in Rstudio. Base on the data after PSM, Kaplan-Meier analysis and established multivariate Cox proportional-hazard model will be performed by survival and survminer package.
Software Used:
RStudio

Project Timeline:

We anticipated start the project In November this year, finish the analysis before 1 Nov 2023, and draft the manuscript for submission before 1 May 2024.

Dissemination Plan:

We plan to submit the project to well-known meetings (GU-ASCO, ESMO) and journals (European Urology, Annals of Oncology)

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/20221031response_to_yoda.pdf