Principal Investigator

First Name: Wataru
Last Name: Fukuokaya
Degree: M.D.
Primary Affiliation: The Jikei University School of Medicine
E-mail: wfukuokaya@gmail.com
Phone number: +81-3-3433-1111
Address: 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo

City: Tokyo
State or Province: Tokyo
Zip or Postal Code: 1050003
Country: Japan

General Information

Key Personnel (in addition to PI):
First Name: Takahiro
Last name: Kimura
Degree: MD, PhD
Primary Affiliation: The Jikei University School of Medicine

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/sv_6m4tghhxg7w7uxe-r_pn9hnleii1tlekf.pdf
https://yoda.yale.edu/system/files/sv_6m4tghhxg7w7uxe-r_2dylmkfu4jfm4p0.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

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Research Proposal

Project Title

Association between proton pump inhibitor use and survival of patients with prostate cancer receiving abiraterone acetate plus prednisone

Narrative Summary:

Accumulated evidence suggests that abiraterone acetate (AA), a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17, exhibits an anti-tumor effect by modifying the gut microbiota. Previous studies have also indicated that proton pump inhibitors (PPIs) can cause significant changes in the gut microbiota; however, the association between PPI use and the effectiveness of AA remains elusive. Therefore, the objective of this study was to investigate the impact of PPI use on the effectiveness of AA in patients with advanced prostate cancer. The results could be employed to improve clinical decision-making for the systemic treatment of advanced prostate cancer.

Scientific Abstract:

Background
Accumulated data suggest that the anti-tumor effect of abiraterone acetate (AA) is, in part, driven by the modulation of the gut microbiota, characterized by the promotion of vitamin K2-producing Akkermansia muciniphila. In contrast, the use of proton pump inhibitors (PPIs) has been associated with decreased A. muciniphila abundance in the gut microbiota.

Objective
To investigate the impact of PPI use in patients with advanced prostate cancer receiving AA.

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 (phase 3 randomized controlled trial [RCT] of AA vs. placebo in chemotherapy-resistant metastatic castration-resistant prostate cancer [mCRPC], N = 1195), COU-AA-302 (phase 3 RCT of AA vs. placebo in chemotherapy-naive mCRPC, N = 1088), and LATITUDE (phase 3 RCT of AA vs. placebo in treatment-naïve metastatic castration-sensitive prostate cancer, N = 1199).

Main Outcome Measures
Progression-free survival is defined as the time from randomization to disease progression in bone and/or soft tissue or death, whichever occurred first. In addition, overall survival and prostate-specific antigen progression-free survival will be determined.

Statistical Analysis
Inverse probability of weighting (IPW) is used to adjust patient characteristics. The IPW-adjusted Kaplan-Meier method will be applied to evaluate the survival distribution. The association between PPI use and outcomes will be evaluated using IPW-adjusted univariable Cox regression models. The interaction terms within these models will also be evaluated.

Brief Project Background and Statement of Project Significance:

It has been reported that gut microbiota participates in hormone metabolism in the host.[1] Furthermore, androgen precursors can reportedly be converted into active androgens, suggesting their involvement in the pathophysiology of prostate cancer.[2]
Abiraterone acetate (AA) is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17 and is widely used to treat locally advanced prostate cancer.[3–5] AA exhibits limited solubility. Reportedly, 50% of

the unaltered parent compound from an administered dose undergoes fecal excretion, indicating that a high amount of AA is exposed to the gut microbiota.[6] A recent study has reported that AA can promote the growth of Akkermansia muciniphila, resulting in increased bacterial biosynthesis of vitamin K2.[7] Vitamin K2 inhibits the growth of androgen-dependent and androgen-independent prostate cancer cells in vitro, and its dietary intake is associated with the risk of advanced prostate cancer.[8,9] Collectively, the effectiveness of AA may be partly driven by its ability to alter the composition of the gut microbiota and increase microbially synthesized vitamin K2.
Proton pump inhibitors (PPIs) are among the most commonly used drug classes, and once initiated, they are continuously used without clear therapeutic intent. In addition, it has been reported that 20 to 50% of patients who receive cancer treatment also utilize PPIs.[10] Like AA, previous studies have indicated that PPI use can be associated with significant changes in gut microbiota.[11,12] Furthermore, PPI use has been associated with a decreased abundance of A. muciniphila, thus suggesting that PPIs might oppose the effect of AA.[13]
Collectively, this study highlights the importance of PPI use in patients with prostate cancer treated with AA, and given the newly available treatment options for patients with advanced prostate cancer, the results may help guide treatment selection.

Specific Aims of the Project:

Increasing evidence suggested that PPI use was associated with the effectiveness of anti-tumor therapeutics.[14,15] This study specifically aims to study the potential role of PPI use on the effectiveness of AA plus prednisone. Our first hypothesis is that PPI use is associated with worse treatment response, measured by radiographic and prostate-specific antigen progression-free survival, of AA plus prednisone. Our second hypothesis is that this association was treatment-specific.

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
Participant-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

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

Outcome measures that will be defined include progression-free survival, overall survival, and prostate-specific antigen progression-free survival, as indicated in the original publications.[3–5]

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

The primary assessed variable is any PPI use within 30 days before and 30 days after treatment initiation. PPI use will be categorized as a dichotomous variable (yes or no).

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

Age (continuous), race, Eastern Cooperative Oncology Group (ECOG) performance status (0 or ?1), baseline

prostate-specific antigen (PSA) (continuous), PSA doubling time (continuous), baseline body mass index (continuous), Gleason score at diagnosis (categorized), reported pain scale (categorized), baseline fatigue severity based on the Brief Fatigue Inventory Question 3 (categorized), previous cancer therapy (categorized), prior local therapy (categorized), prior taxane (no or yes), castration status (castration-sensitive or castration-resistance), disease extent (categorized), number of bone metastases (categorized), presence of liver metastasis (no or yes), presence of nodal metastasis (no or yes), presence of visceral metastasis (no or yes), time from GnRH agonist/antagonist to first dose (continuous), analgesic use (no or yes), antibiotic use (no or yes).

Statistical Analysis Plan:

Descriptive statistics will be used to describe patient characteristics. Inverse probability of weighting (IPW) will be used for the adjustment of covariates. Unweighted and weighted patient characteristics will be stratified according to PPI use.
The association between PPI use and patient characteristics will be assessed using an unweighted logistic regression model. IPW-adjusted Kaplan-Meier curves will be calculated to compare survival between PPI users and non-users. The IPW-adjusted Cox regression model will be used to evaluate the hazard ratio for PPI use on clinical outcomes. Furthermore, heterogeneity of treatment effects according to patient characteristics and treatment (AA or placebo) will be examined by testing the interaction terms within the IPW-adjusted Cox regression models. The association between PPI use and adverse events or complications that occur during treatment will also be evaluated.
Software Used:
RStudio
Project Timeline:

Day 0: Approval of the project
Day30: Data transfer
Day 60: Data processing
Day 90: Data analysis
Day 120: Manuscript writing
Day 180: Manuscript submission

Dissemination Plan:

The findings of this project are expected to result in the development of a manuscript suitable for publication in a urologic oncology journal. In addition, the results will be presented at appropriate urologic oncology conferences.

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