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Project Funding Source: JSPS KAKENHI
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/coi_fukuokaya_0.pdf
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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. NCT02489318 - 56021927PCR3002 - A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects With Metastatic Hormone-sensitive Prostate Cancer (mHSPC)

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

Research Proposal

Project Title

Patterns of disease progression in patients with metastatic, castration-sensitive prostate cancer

Narrative Summary:

In metastatic, castration-sensitive prostate cancer (mCSPC), treatment effectiveness is commonly assessed by prostate-specific antigen progression and radiographic progression. However, inconsistencies often arise between these events, especially in patients with mCSPC treated with the combination of androgen deprivation therapy and androgen receptor axis-targeted agents. Given the potential implications, gaining a deeper understanding of disease progression in this population is crucial. In this study, we use data from the TITAN trial to investigate the patterns of disease progression in patients with mCSPC treated with apalutamide.

Scientific Abstract:

Background
Prostate-specific antigen (PSA) levels and radiographic examinations were common tools for treatment monitoring in patients with metastatic, castration-sensitive prostate cancer (mCSPC). Evidence showed a frequent discordance PSA progression and radiographic progression in patients with mCSPC, especially those treated with androgen deprivation therapy (ADT) and androgen receptor axis-targeted agents (ARATs). However, the patterns of disease progression, and their associations with overall survival (OS) in patients with mCSPC treated with ADT plus apalutamide are not well-characterized.

Objective
To investigate the patterns of disease progression in patients with mCSPC receiving ADT plus apalutamide.

Study Design
A post-hoc analysis, using data on the TITAN trial.

Participants
Patients with mCSPC, treated in combination with ADT and apalutamide or placebo who progressed as measured by PSA levels or radiographic examinations.

Main Outcome Measures
PSA progression-free survival (PSA-PFS), radiographic progression-free survival (RPFS), and OS as per the trial protocol.

Statistical Analysis
Descriptive statistics were used to summarize the types and patterns of disease progression. Particularly, baseline characteristics and the patterns of radiographic progressions with or without concurrent PSA progression were examined. The concordance of PSA-PFS and RPFS with OS were tested using c-statistics.

Brief Project Background and Statement of Project Significance:

Androgen deprivation therapy (ADT), either alone or in combination with androgen receptor axis-targeted agents (ARATs) or cytotoxic chemotherapy, is the standard of care for advanced or metastatic prostate cancer.[1] The response to treatment is typically monitored through prostate-specific antigen (PSA) levels and radiographic examinations. However, in metastatic, castration-resistant prostate cancer (mCRPC), relying solely on PSA monitoring has proven insufficient for monitoring disease activity. Evidence suggests that a quarter of patients experience radiographic progression without corresponding PSA progression, as defined by the prostate cancer working group 2 definition.[2,3] Consequently, current guidelines recommend a combination of regular radiographic examinations and PSA measurements for assessing patients with mCRPC.[1] A majority of experts at the Advanced Prostate Cancer Consensus Conference Current also recommend regular radiographic examinations, regardless of PSA levels, for this population.[4]
In contrast, for metastatic, castration-sensitive prostate cancer (mCSPC), the current guidelines do not mandate regular radiographic examinations unless patients maintain stable PSA levels and are asymptomatic.[1] However, evidence suggest that discrepancies between PSA progression and radiographic progression also occur in patients with mCSPC treated with ADT.[5,6] Furthermore, a post-hoc analysis of data from a randomized controlled trial showed that this discrepancy can be more pronounced in patients treated with the combination of ADT and ARATs

than in those treated with ADT and placebo.[5] However, the applicability of these findings to patients with mCSPC treated with ADT and other ARATs remains unclear. In this study, we use data from the TITAN trial to investigate the patterns of disease progression in patients with mCSPC treated with ADT plus apalutamide. Elucidating the patterns of disease progression in this population could facilitate the optimization of treatment strategies for patients with mCSPC receiving intensified systemic treatment.

Specific Aims of the Project:

The primary aim of this study is to assess the patterns of disease progression in patients with metastatic, castration-sensitive prostate cancer treated with androgen deprivation therapy (ADT) and apalutamide. We propose the following hypotheses for this study:
1. Radiographic progression in the absence of prostate specific antigen (PSA) progression is more common in patients treated with the combination of ADT and apalutamide than in those treated with ADT plus placebo.
2. Radiographic progression without corresponding PSA progression is a worse prognostic factor for radiographic progression-free survival.
3. Baseline characteristics, specifically the site of baseline metastatic location, differ between patients developing radiographic progression with corresponding PSA progression and those developing radiographic progression without corresponding PSA progression.

What is your Study Design?:

Individual trial analysis

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:

Inclusion criteria: all patients in this trial
Exclusion criteria: missing outcome data

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

Radiographic progression, prostate-specific antigen progression, and all-cause mortality as per the trial protocol.[7]

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

The primary variable is radiographic progression, with the prostate-specific antigen (PSA) kinetics serving as a secondary variable. Values of PSA are assessed at three specific time points: the day when the nadir value is achieved, and the days within 30 days before and after confirming radiographic progression.

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

The following variables will be included as covariates: age (categorical), race (categorical), Eastern Cooperative Oncology Group performance status (categorical), baseline prostate-specific antigen (continuous), Gleason score at diagnosis (categorical), reported pain scale (categorical), prior local therapy (categorical), presence of liver metastasis (categorical), presence of visceral metastasis (categorical), metastasis stage at initial diagnosis (categorical), baseline hemoglobin (continuous), baseline albumin (continuous), baseline alkaline phosphatase (continuous), and baseline lactate dehydrogenase (continuous), previous docetaxel use (categorical), and baseline disease volume (categorical).

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Statistical Analysis Plan:

Descriptive statistics will be employed to describe baseline characteristics, prostate-specific antigen (PSA) levels at radiographic progression, and the patterns of disease progression. Time-to-event outcomes will be depicted with Kaplan-Meier curves and compared using the log-rank test. The concordance of radiographic progression-free survival and PSA progression-free survival with overall survival will be determined using Harrell's concordance index. Hazard ratios for all-cause mortality will be computed using Cox regression models, treating the patterns of disease progression as a time-dependent variable.
Software Used:
RStudio
Project Timeline:

Day 0: Approval of the project
Day 60: Data transfer
Day 120: Data processing
Day 150: Data analysis
Day 180: Manuscript writing
Day 210: Manuscript submission

Dissemination Plan:

The results of this project are expected to result in the development of a manuscript suitable for publication in a uro-oncology journal. Results will be presented at appropriate uro-oncology conferences.

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