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Requires Data Access? No

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?: Twitter

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/01/coi_mori.pdf
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https://yoda.yale.edu/wp-content/uploads/2024/01/coi_fukuokaya.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. NCT02489318 - 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

Volume of bone metastasis and outcomes of apalutamide in patients with metastatic castration-sensitive prostate cance

Narrative Summary:

In metastatic castration-sensitive prostate cancer (mCSPC), assessing disease volume is crucial for prognosis and treatment choices. The CHAARTED criteria, evaluating disease volume via visceral metastases or ≥4 bone lesions (one outside vertebral bodies/pelvis), are widely recognized. While the value of these criteria is evidenced, it is unclear how specifically the number of baseline bone metastases affects survival, particularly in patients receiving apalutamide. Our study aims to determine the effect of the number of baseline bone metastases on survival in patients with mCSPC receiving ADT with or without apalutamide in the TITAN trial.

Scientific Abstract:

Background
Disease volume, determined by visceral involvement and the number of bone metastases, is often evaluated to determine prognosis in patients with metastatic castration-sensitive prostate cancer (mCSPC). The precise prognostic impact and the ideal threshold for the number of baseline bone metastases in mCSPC remain uncertain, particularly in patients treated with apalutamide.

Objective
To investigate the association between the number of bone metastases and outcomes of apalutamide plus androgen deprivation therapy (ADT) in patients with mCSPC.

Study Design
A secondary analysis of the TITAN trial.1

Participants
Patients with mCSPC, receiving a combination of ADT and apalutamide or matched placebo.

Main Outcome Measures
Radiographic progression-free survival (RPFS) and overall survival (OS) as per the trial protocol. RPFS was specified as the interval from the date of randomization and the date of earliest occurrence of either documented disease progression through imaging or death. A diagnosis of radiographic progressive disease was given if the patient showed progression of soft-tissue lesions, as detected by computed tomography or magnetic resonance imaging, or the presence of new bone lesions identified through bone scanning. Furthermore, OS was characterized as the interval from the date of randomization and the date of all-cause death.

Statistical Analysis

The association between the number of baseline bone metastases and relevant baseline covariates will be assessed using multiple linear regression analysis. We will use restricted cubic splines in multivariable Cox proportional hazards regression models to evaluate a continuous non-linear association between the number of baseline bone metastases and RPFS and OS. Additionally, we will examine the effect of the addition of apalutamide to ADT on the number of baseline bone metastases, using the same models with the inclusion of interaction terms.

Brief Project Background and Statement of Project Significance:

The introduction of new androgen receptor pathway inhibitors (ARPis), such as apalutamide, abiraterone acetate, darolutamide, and enzalutamide, has revolutionized the treatment of metastatic prostate cancer. These agents, initially used in later stages of the disease, are now used in metastatic castration-sensitive prostate cancer (mCSPC).1–4 In mCSPC, disease volume is typically assessed by evaluating both the presence of baseline visceral metastasis and the number of baseline bone metastases. This approach stems from the CHAARTED trial, which investigated the efficacy of adding docetaxel to androgen deprivation therapy (ADT) in mCSPC.5 Although these criteria were first evaluated in mCSPC managed with ADT, with or without docetaxel, the impact of disease volume on treatment outcomes has been extensively studied in patients treated with various ARPis.1,2,6 The prognostic effect of baseline visceral metastasis on survival in patients with mCSPC is well-established;7,8 however, the detailed effect of the number of baseline bone metastases on survival remain uncertain. This study aims to evaluate the effect of the number of baseline bone metastases on outcomes in patients with mCSPC treated with apalutamide and ADT. Further, we will also study whether the effect of adding apalutamide on ADT differs based on the number of baseline bone metastases. The findings of this study may refine the criteria for assessing disease volume and suggest the potential for treatment de-intensification in specific groups of patients with mCSPC.

Specific Aims of the Project:

The primary aim of this study is to assess the effect of baseline bone metastasis on outcomes in patients with metastatic castration-sensitive prostate cancer treated with androgen deprivation therapy (ADT) and apalutamide. Additionally, we also examine if the effect of the addition of apalutamide on ADT differs based on the number of baseline bone metastases.

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-free survival (RPFS) and overall survival (OS) as per the trial protocol. RPFS was specified as the interval from the date of randomization and the date of earliest occurrence of either documented disease progression through imaging or death. A diagnosis of radiographic progressive disease was given if the patient showed progression of soft-tissue lesions, as detected

by computed tomography or magnetic resonance imaging, or the presence of new bone lesions identified through bone scanning. Furthermore, OS was characterized as the interval from the date of randomization and the date of all-cause death.

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

The primary variable in our study is the number of baseline bone metastases. We consider this variable continuously to evaluate its non-linear association with the outcomes of androgen deprivation therapy, both with and without apalutamide. Should the data indicate clinical relevance, we will categorize the primary variable accordingly.

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), 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), baseline hemoglobin (continuous), baseline lactate dehydrogenase (continuous), and previous docetaxel use (categorical).

Statistical Analysis Plan:

Descriptive statistics will describe baseline characteristics and the number of baseline bone metastases. We will evaluate the association between the number of baseline bone metastases and relevant baseline covariates using multiple linear regression models. Kaplan-Meier curves will depict time-to-event outcomes, and we will compare these using the log-rank test. To examine a non-linear association between the count of baseline bone metastases and treatment outcomes, we will use multivariable Cox proportional hazards regression models with a restricted cubic spline function. Additionally, we will investigate if the effect of adding apalutamide to androgen deprivation therapy varies depending on the number of baseline bone metastases, incorporating interaction terms into the same models. The results will be presented as a function of the count of baseline bone metastasis on the hazard ratio scale.

Software Used:

R

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.

Bibliography:

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6. Hussain M, Tombal B, Saad F, et al. Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer by Disease Volume and Risk Subgroups in the Phase III ARASENS Trial. *J Clin Oncol*. 2023;41(20):3595-3607.
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8. Yanagisawa T, Rajwa P, Kawada T, et al. Efficacy of Systemic Treatment in Prostate Cancer Patients With Visceral Metastasis: A Systematic Review, Meta-analysis, and Network Meta-analysis. *J Urol*. 2023;210(3):416-429.