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SCOPUS ID:
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?: PubMed

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/11/1SV_57KskaKADT3U9Aq-R_4fRaL3K5lNkJj7r.pdf
https://yoda.yale.edu/wp-content/uploads/2025/11/SV_57KskaKADT3U9Aq-R_9nd5nBhdAdAFeYU.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. NCT01946204 - ARN-509-003 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men With Non-Metastatic (M0) Castration-Resistant Prostate Cancer

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

Research Proposal

Project Title

Utility of Whole Pelvic Radiotherapy in the Era of Novel Hormonal Agents: A Post-hoc Analysis of the SPARTAN Trial

Narrative Summary:

This study aims to understand if the way prostate cancer patients were treated with radiation in the past affects how well they respond to the drug Apalutamide later in their disease course. Specifically, we want to know if patients who had radiation to their whole pelvis respond differently to Apalutamide compared to those who only had radiation to the prostate gland. This will help doctors decide if extensive radiation is necessary when potent drugs like Apalutamide are available.

Scientific Abstract:

Background: The SPARTAN trial established Apalutamide (APA) as a standard of care for non-metastatic Castration-Resistant Prostate Cancer (nmCRPC). While APA exerts potent systemic control, it remains unknown whether its efficacy is modulated by the extent of prior local therapy--specifically, Elective Whole Pelvic Radiotherapy (WPRT) versus Prostate-Only Radiotherapy (PORT).

Objective: To assess the heterogeneity of APA treatment effect on Metastasis-Free Survival (MFS) contingent upon the prior radiotherapy field (WPRT vs. PORT).

Study Design: Post-hoc subgroup analysis of the randomized Phase 3 SPARTAN trial (NCT01946204).

Participants: A subset of the Intent-to-Treat population with a verifiable history of prior external beam radiotherapy. Patients will be stratified into WPRT or PORT cohorts based on medical history coding and available radiation dosimetry records.

Primary and Secondary Outcome Measure(s): Primary: MFS. Secondary: Overall Survival (OS) and the comparative incidence of late radiation-associated gastrointestinal/genitourinary toxicity.

Statistical Analysis: Multivariable Cox proportional hazards models will be used to estimate Hazard Ratios (HR) for MFS within WPRT and PORT subgroups. A formal treatment-by-subgroup interaction test will be conducted to evaluate effect modification. Propensity score weighting will be employed to adjust for baseline confounding by indication regarding the initial choice of radiation field.

Brief Project Background and Statement of Project Significance:

Background and Rationale: The optimal radiation field for high-risk localized prostate cancer--Elective Whole Pelvic Radiotherapy (WPRT) versus Prostate-Only Radiotherapy (PORT)--remains a subject of debate. While WPRT aims to eradicate occult pelvic lymph node micrometastases, it is associated with increased gastrointestinal toxicity. The advent of Next-Generation Androgen Receptor Signaling Inhibitors (ARSIs), such as Apalutamide, has introduced a potent systemic mechanism for controlling microscopic disease.
The SPARTAN trial (NCT01946204) demonstrated the superior efficacy of Apalutamide in high-risk nmCRPC patients. This population, characterized by rapid PSA doubling times despite castrate testosterone levels, represents a cohort where prior local therapies have biologically failed. By retrospectively analyzing the SPARTAN data, we can evaluate whether the "type" of prior local failure (i.e., failure after WPRT vs. failure after PORT) acts as an effect modifier for Apalutamide. This analysis has significant implications for de-escalation strategies in the primary setting: if Apalutamide effectively "rescues" patients regardless of their prior radiation field, it may support the omission of initial WPRT in the era of intensified systemic therapy.

Specific Aims of the Project:

1.Primary Aim: To assess the Heterogeneity of Treatment Effect (HTE) of Apalutamide on Metastasis-Free Survival (MFS) across subgroups defined by prior radiotherapy extent (Prior WPRT vs. Prior PORT).
2.Secondary Aim: To compare the cumulative incidence of late Grade >=2 gastrointestinal (GI) and genitourinary (GU) toxicities in the Apalutamide arm, stratified by prior radiation field, to evaluate the long-term toxicity burden of combined modality approaches.

Study Design:

Individual trial analysis

What is the purpose of the analysis being proposed? Please select all that apply.

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Research Methods

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

1. Data Source The study utilizes Individual Participant Data (IPD) exclusively from the SPARTAN trial (NCT01946204), accessed via the YODA Project's secure data environment. No external datasets will be pooled with this analysis.

2. Study Sample Derivation We will derive a retrospective cohort from the SPARTAN Intent-to-Treat (ITT) population to specifically evaluate patients with a history of definitive local radiotherapy.

3. Explicit Inclusion Criteria

Population: All subjects randomized in the SPARTAN trial (NCT01946204).

Prior Radiotherapy Exposure: Subjects must have a documented history of prior External Beam Radiotherapy (EBRT) for prostate cancer. Ascertainment of prior RT will be based on:

Records in the Medical History (MH), Concomitant Procedures (CP), or Radiotherapy (RT) domains.

Availability of sufficient descriptive text (e.g., "whole pelvis", "prostate bed") OR dosimetric data (e.g., dose/fractionation records) to permit classification into either the Whole Pelvic Radiotherapy (WPRT) or Prostate-Only Radiotherapy (PORT) subgroups.

4. Explicit Exclusion Criteria

No Prior RT: Subjects managed exclusively with Radical Prostatectomy or primary Androgen Deprivation Therapy (ADT) who have no record of ever receiving radiotherapy to the prostate or pelvis.

Unclassifiable Radiation Field: Subjects with ambiguous radiotherapy records where the specific treatment volume cannot be reliably ascertained even after reviewing all available text descriptions and dose proxies (e.g., generic entry of "Radiation" without anatomic specification or dose details), to prevent misclassification bias.

5. External Data and Analysis Platform

External Data: None. We do not plan to use data from studies other than the requested SPARTAN trial.

Platform: All analyses will be conducted within the YODA Project's secure remote access environment (SAS/R studio) without aggregating summary results from outside sources.

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

1. Primary Outcome Measure Metastasis-Free Survival (MFS):

Definition: Consistent with the primary endpoint of the parent SPARTAN trial. Defined as the time from the date of randomization to the date of first evidence of distant metastasis (new bone or soft tissue lesions) as assessed by Blinded Independent Central Review (BICR), or death from any cause, whichever occurred first.

Categorization: Analyzed as a time-to-event variable. Patients without an event will be censored at the date of last adequate disease assessment.

2. Secondary Outcome Measures A. Overall Survival (OS):

Definition: Defined as the time from randomization to the date of death from any cause.

Categorization: Analyzed as a time-to-event variable.

B. Late Radiation-Associated Toxicity (Safety Endpoint):

Definition: Given the focus on radiation fields, we will specifically evaluate the cumulative incidence of late Gastrointestinal (GI) and Genitourinary (GU) adverse events.

Categorization: Adverse events will be identified from the AE dataset using specific MedDRA Preferred Terms (e.g., proctitis, diarrhea, rectal hemorrhage, cystitis, hematuria). These will be categorized based on NCI CTCAE version 4.0 severity:

Clinically Significant: Grade >=2.

Mild/None: Grade 0-1.

We will compare the incidence rates of Grade >=2 toxicities between the Prior-WPRT and Prior-PORT subgroups to assess the long-term safety burden.

C. Time to Symptomatic Progression:

Definition: Time from randomization to the development of a skeletal-related event, pain progression/worsening, or need for surgical intervention for tumor.

3. Changes to Outcomes We do not anticipate deviations from the standard definitions used in the SPARTAN trial. However, the "Late Radiation-Associated Toxicity" is a composite safety endpoint specifically constructed for this post-hoc analysis by filtering relevant preferred terms, distinct from the general safety reporting of the parent trial.

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

The analysis involves two main independent variables and their interaction:

1. Randomized Treatment Assignment: This is the primary intervention variable as defined in the original SPARTAN trial. It will be categorized as a binary variable:

Apalutamide Group: Patients randomized to receive Apalutamide plus ADT.

Placebo Group: Patients randomized to receive Placebo plus ADT.

2. Extent of Prior Radiotherapy (Prior_RT_Field): This is the novel predictor of interest for this post-hoc analysis. It will be defined as a categorical (binary) variable derived from the 'Medical History' (MH), 'Concomitant Procedures' (CP), or 'Radiotherapy' datasets. Patients with a history of prior definitive radiotherapy will be categorized into:

Whole Pelvic Radiotherapy (WPRT): Defined by the presence of specific keywords in the medical history description (e.g., "whole pelvis", "pelvic lymph nodes", "nodal irradiation") OR inferred from radiation dose records if available (e.g., documentation of a treatment phase delivering 45--50.4 Gy to a pelvic volume).

Prostate-Only Radiotherapy (PORT): Defined by descriptions indicating treatment confined to the prostate gland, prostate bed, or fossa (e.g., "prostate only", "prostate bed") without documentation of pelvic nodal irradiation.

Definition of Independent Effect: The study focuses on the interaction term between these two variables (Treatment x Prior_RT_Field). We aim to test whether the independent variable Prior_RT_Field acts as an effect modifier on the primary outcome (Metastasis-Free Survival), specifically determining if the Hazard Ratio (HR) of Apalutamide differs significantly between the WPRT and PORT subgroups.

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 extracted to characterize the study cohort and utilized as covariates for multivariable adjustment (Cox proportional hazards models) and propensity score weighting to control for confounding by indication:

1. Patient Demographics:

Age: Continuous variable (years) and categorical (<75 vs. >=75 years).

ECOG Performance Status: Categorical (0 vs. 1).

Race/Ethnicity: Categorical (White, Black, Asian, Other).

2. Clinical Characteristics at Initial Diagnosis (Key Confounders): These are critical for adjusting for selection bias, as patients with higher-risk features were more likely to receive WPRT historically.

Initial Gleason Score: Categorical (6 months). This is a major prognostic factor in the SPARTAN trial.

Use of Bone-Sparing Agents: Binary (Yes/No).

4. Safety Outcomes (Secondary Endpoints):

Gastrointestinal (GI) Toxicity: Defined based on adverse event terms (e.g., diarrhea, proctitis, rectal hemorrhage) graded according to CTCAE criteria. Categorized as Grade 0-1 (Low) vs. Grade >=2 (Clinically Significant).

Genitourinary (GU) Toxicity: Defined based on adverse event terms (e.g., cystitis, hematuria, urinary frequency). Categorized as Grade 0-1 vs. Grade >=2.

All covariates will be assessed for missingness. Variables with >20% missing data will be excluded from the primary multivariable model or handled via multiple imputation if appropriate.

Statistical Analysis Plan:

1.Descriptive Analysis: Baseline characteristics will be compared between the Prior-WPRT and Prior-PORT subgroups using Chi-square tests or t-tests to assess potential selection bias in the original administration of radiotherapy.
2.Survival Analysis:
a.Kaplan-Meier survival curves for MFS will be plotted for Apalutamide vs. Placebo within each subgroup (WPRT vs. PORT).
b.A multivariable Cox proportional hazards model will be constructed including the interaction term: Treatment (APA vs PBO) * Prior_RT_Field (WPRT vs PORT).
c.A p-value < 0.10 for the interaction term will be considered suggestive of a differential treatment effect.
3.Sensitivity Analysis: To control for confounding by indication (since prior WPRT is often prescribed to higher-risk patients), we will perform a Propensity Score Adjusted analysis, weighting the model by the inverse probability of receiving WPRT based on initial diagnostic characteristics (Gleason, T-stage, N-stage).
4.Software: Analyses will be performed using R and Python.

Software Used:

Python, R, RStudio

Project Timeline:

We anticipate a 12-month project duration from the date of data access provision.

1. Project Start & Data Setup (Months 1-2):

Anticipated Start Date: Immediately upon execution of the Data Use Agreement (DUA) and provision of remote access credentials.

Initial data quality check and familiarization with the SPARTAN dataset structure.

Cohort selection: Filtering the ITT population for patients with prior radiotherapy.

2. Data Harmonization & Variable Extraction (Months 3-4):

Critical Step: Execution of text-mining algorithms on 'Medical History' and 'Concomitant Procedures' domains to categorize the "Prior Radiotherapy Field" (WPRT vs. PORT).

Cleaning of covariates and handling of missing data.

3. Statistical Analysis (Months 5-7):

Descriptive statistics and baseline characteristic comparisons.

Execution of Propensity Score Matching (PSM) or Weighting (IPTW).

Analysis Completion Date: Estimated at Month 7. This includes primary survival analysis (Cox models), interaction testing, and secondary safety analysis.

4. Manuscript Preparation (Months 8-10):

Generation of final publication-quality tables and figures (Forest plots, Kaplan-Meier curves).

Drafting of the manuscript.

Internal review and revision by the study team.

5. Submission & Reporting (Months 11-12):

Manuscript Submission Date: Targeted for Month 11 (Submission to a peer-reviewed journal such as JAMA Oncology, European Urology, or similar).

Results Reported to YODA: Month 12. We will upload the abstract, manuscript draft, or published citation to the YODA platform as required before the expiration

Dissemination Plan:

The primary product of this research will be a high-quality, peer-reviewed manuscript reporting the interaction between prior radiotherapy fields (WPRT vs. PORT) and the efficacy of Apalutamide.

Target Audience: Our findings will be of immediate clinical relevance to a multidisciplinary audience, specifically Radiation Oncologists, Urologic Oncologists, and Medical Oncologists. The results may directly influence decision-making regarding the necessity of elective pelvic radiation in the primary setting, a topic of high current interest.

Target Journals: Given the high profile of the parent SPARTAN trial and the clinical implications of this sub-analysis, we intend to target high-impact specialty journals.

Primary Targets: European Urology, JAMA Oncology, or Journal of Clinical Oncology (JCO).

Secondary Targets: International Journal of Radiation Oncology, Biology, Physics (IJROBP) or Clinical Cancer Research.

Conference Presentations: Prior to or concurrent with manuscript submission, we plan to submit an abstract for oral or poster presentation at major international scientific meetings, specifically:

ASCO Genitourinary Cancers Symposium (ASCO GU): The premier venue for GU medical oncology.

ASTRO Annual Meeting: The leading forum for radiation oncology, where the debate on WPRT vs. PORT is most active.

Finally, we commit to sharing the final publication and a summary of results with the YODA Project to ensure transparency and contribute to the open science ecosystem.

Bibliography:

1. Primary SPARTAN Trial Publication (Efficacy & Safety): Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*. 2018;378(15):1408-1418. **DOI:** 10.1056/NEJMoa1715546 **URL:** https://www.nejm.org/doi/full/10.1056/NEJMoa1715546

2. SPARTAN Trial Final Analysis (Overall Survival): Small EJ, Saad F, Chowdhury S, et al. Final Survival Results From SPARTAN, a Phase 3 Study of Apalutamide (APA) Versus Placebo (PBO) in Patients With Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC). *Eur Urol*. 2021;79(1):81-84. **DOI:** 10.1016/j.eururo.2020.08.002 **URL:** https://www.europeanurology.com/article/S0302-2838(20)30678-2/fulltext

3. POP-RT Trial (The basis for WPRT vs PORT debate): Murthy V, Maitre P, Kannan S, et al. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. *J Clin Oncol*. 2021;39(11):1234-1242. **DOI:** 10.1200/JCO.20.03282 **URL:** https://ascopubs.org/doi/full/10.1200/JCO.20.03282

4. RTOG 9413 Trial (Historical context for WPRT): Roach M 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic to prostate-only radiotherapy and neoadjuvant to adjuvant

combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol*. 2003;21(10):1904-1911. **DOI:** 10.1200/JCO.2003.05.004 **URL:** https://ascopubs.org/doi/10.1200/JCO.2003.05.004

5. ATLAS Trial Abstract (Context for Apalutamide + RT): Sandler HM, Fizazi K, Cattamanchi A, et al. ATLAS: A phase 3 randomized, double-blind, placebo-controlled study of apalutamide (APA) versus placebo (PBO) in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy (RT). *J Clin Oncol*. 2016;34(15_suppl):TPS5083. **DOI:** 10.1200/JCO.2016.34.15_suppl.TPS5083 **URL:** https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.TPS5083