Principal Investigator

First Name: Shawn
Last Name: Malone
Degree: M.D., FRCPC
Primary Affiliation: Radiation Medicine Program, The Ottawa Hospital Cancer Centre, University of Ottawa
E-mail: smalone@toh.ca
Phone number: 613-737-7700
Address: 501 Smyth Road, Ottawa, ON, Canada
501 Smyth Road
City: Ottawa
State or Province: Ontario
Zip or Postal Code: K1H 8L6
Country: Canada

General Information

Key Personnel (in addition to PI):
First Name: Soumyajit
Last name: Roy
Degree: MBBS, MSc.
Primary Affiliation: Rush University Medical Center

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/coi_roy_yoda.pdf
https://yoda.yale.edu/system/files/coi_form_sm.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

Impact of Prior Local Therapy on Outcome in Men with non-metastatic Castrate Resistant Prostate Cancer

Narrative Summary:

Preclinical or animal studies have shown that primary local therapy directed to prostate (like removal of prostate or radiation therapy) triggers changes at cellular level in the cancer cells. However, it is unknown whether such changes translate into any clinically meaningful difference in outcomes when systemic therapies are initiated after progression to a stage when the disease is refractory to hormone therapy. This secondary analysis of SPARTAN will provide clear insight on whether receipt of prior local therapy affect outcome including response to subsequent lines of therapy in men with prostate cancer whose disease is refractory to hormone therapy.

Scientific Abstract:

Background: Preclinical studies suggest that receipt of definitive local therapy at the time of diagnosis might bear substantial effect on subsequent systemic therapy in prostate cancer. However, these findings from preclinical studies have never been replicated in the clinical studies especially in a setting where the disease is castrate resistant but non-metastatic.

Objectives: We propose a secondary analysis of SPARTAN trial to determine if receipt of prior local therapy (radical prostatectomy [RP] or radiation therapy [RT] or both) or its type play an effect modifying role on treatment effect from apalutamide on metastasis-free survival (MFS) and overall survival (OS) in patients with non-metastatic castrate resistant prostate cancer (nmCRPC). We also plan to compare OS and MFS in patients treated with prior local therapy compared to those who had no prior local therapy.
Design and Participants: Secondary analysis with patients in the SPARTAN trial (NCT01946204).
Main outcome measures: The primary endpoint will be MFS. Secondary outcome will be OS.
Main exposure variable: Receipt of prior local therapy (RP or RT or both) vs no local therapy (LT).
Statistical Plan: For MFS and OS, separate multivariable Cox regression models will be applied to determine the adjusted effect of local therapy after adjustment for treatment arm (apalutamide vs placebo), duration of androgen deprivation therapy (ADT), Gleason score, tumor stage, PSA, and nodal stage at initial diagnosis, PSA at enrollment, duration of ADT before enrollment in trial and the time interval between initial diagnosis to randomization. An interaction term between the treatment arm and local therapy will be incorporated into the Cox models which will provide information on presence of any significant effect modification by local therapy on the effect of randomized treatment on these endpoints. Similar analyses will be performed for type of prior local therapy. Grambsch Therneau test will be applied to verify proportionality assumption of the Cox models.

Brief Project Background and Statement of Project Significance:

Combination of prostate directed local therapy [LT] (either radical prostatectomy [RP] or radiation therapy (RT) or both) with androgen deprivation therapy (ADT) is the definitive treatment option for men with localized prostate cancer (LPCa).[1,2] Despite this, a proportion of patients especially those with high-risk vs. locally advanced patients eventually develop recurrence, castrate resistance even in absence of distant metastasis. [3,4] At this stage, systemic treatment remains the mainstay of management. [5] Non-metastatic castrate resistant prostate cancer is a subgroup of this patient population that are characterized by an increase in prostate-specific antigen (PSA) concentration despite castrate level of testosterone and no evidence of distant metastasis on conventional imaging. [6] Current treatment strategies for this group of patients include novel androgen receptor targeting agents such as apalutamide, darolutamide, or enzalutamide. [6–9]

Preclinical studies have shown that fractionated RT can induce neuroendocrine differentiation in prostate cancer by increasing the nuclear content of phospho-CREB (cyclic AMP–response element binding protein) and cytoplasmic accumulation of ATF2 (activating transcription factor 2). [10] This has significant implications in progression of cancer, androgen-independent growth, and it ultimately portends poor prognosis. In contrast, minimal residual disease after RP could give rise to treatment-resistant clones that can lead to poor response to adjuvant or salvage therapy. [11] In a small Japanese study, initial curative LT modality was a significant predictor of castration resistance based on a multivariable regression. [12] However, there remains no robust evidence to support the premise of prior LT affecting response to novel anti-androgen therapy in nmCRPC.
SPARTAN is a phase III randomized controlled trial in which nmCRPC patients were randomly assigned at 2:1 ratio to receive apalutamide vs placebo in addition to ADT. Apalutamide was associated with significant improvement in metastasis-free survival (MFS) (hazard ratio [HR]: 0.28 with 95% confidence interval [CI]: 0.23-0.35)14. In an updated analysis with median follow-up of 52 months, median overall survival (OS) was markedly longer with

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apalutamide versus placebo, reaching prespecified statistical significance (HR: 0.78 [0.64–0.96]). [7] However, it is unknown if prior LT played an effect modifying role on the treatment effect from apalutamide.
Herein we propose an exploratory analysis of SPARTAN study to compare the treatment effect from first line apalutamide in patients treated with prior LT and by the type of prior LT (RP vs. RT).

The findings of this proposed study will be important to understand whether the response to subsequent lines of therapy in men with nmCRPC depends when the cancer is hormone refractory depend on the receipt of and type of prostate directed LT at the time of diagnosis. Furthermore, this will also clarify if there is any association of receipt of prior LT with MFS and OS in these patients. Overall, these information will be useful to tailor treatment for this patient population in the future.

Specific Aims of the Project:

Aim 1: if the response to first line androgen receptor axis targeted therapy (ARAT) in nonmetastatic castrate resistant prostate cancer (nmCRPC) vary based on receipt of prior local therapy (LT) to prostate?
We will determine if the treatment effect from first line ARAT on MFS and OS differ among patients who received prior local LT (radical prostatectomy [RP] or radiation therapy [RT] or both) to prostate versus those who did not receive any prior LT to prostate. Furthermore, we will also determine if the treatment effect on this outcome vary depending on type of prior LT (RP vs. RT vs. both).

Aim 2: Does receipt of prior local therapy has any association with oncologic outcome in patients with chemotherapy naive mCRPC?
To investigate this, we will compare MFS and OS in patients treated with prior LT to prostate compared to those who did not. Finally we will perform a separate analysis to determine if the modality of the prior local therapy (RP vs. RT vs. both) has any association with MFS and OS.

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:

SPARTAN trial (NCT01946204) dataset - both raw and derived

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

Primary Outcome:
Metastasis-free survival (MFS): MFS will be determined as time from randomization to incidence of distant metastasis or death.
Overall Survival (OS): OS will be determined as time from randomization to incidence of death from any cause.

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

Receipt of prior local therapy (radical prostatectomy or radiotherapy to prostate or both) vs no local therapy.
Additional subgroup analyses will be done to compare patients treated with radical prostatectomy and those treated with radiotherapy to prostate.

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

your study:

Baseline Factors:
- Treatment arm: Categorical
- Race: Categorical
- Region of study: Categorical
- Age, height, weight: Continuous
- Gleason Score at initial diagnosis: Ordinal
- Prior surgery i.e. prostatectomy: yes/no (categorical)
- Date of prior prostatectomy (if available)
- Prior radiation therapy: yes/no (categorical)
- Dates and dose of prior radiation therapy
- ECOG PS: Ordinal (0-2)
- Date of randomization (date format) – to calculate all endpoints
- Prior systemic treatment (ADT) – yes/no (categorical)
- Testosterone at the time of study entry – continuous numeric variable
- Tumor stage at diagnosis – categorical
- Nodal stage at diagnosis - categorical
- PSA at diagnosis - continuous

Baseline and Post-Baseline Variables:
- PSA at time of study entry: continuous variable
- PSA doubling time at study entry: continuous variable
- Time of distant metastasis (date format)
- Distant metastasis (yes/no) - categorical
- Site of metastasis (descriptive)
- Deaths (yes/no) – categorical
- Time of death (date format) and cause of death

Statistical Analysis Plan:

Descriptive statistics will be used to characterize the data in the study, including means, medians, and analysis of variance and Wilcoxon signed rank for continuous variables and frequency tables and chi-square test for categorical variables. MFS and OS will be estimated using Kaplan-Meier methods. Multivariable Cox regression will be applied to estimate adjusted association of the primary local therapy adjusting for adjusting for age at randomization, treatment arm, duration of ADT, Gleason score at initial diagnosis, tumor stage at initial diagnosis, nodal stage at initial diagnosis, PSA at diagnosis and at the time of study entry and PSA-doubling time at the time of study entry. Kaplan-Meier product limit method will be used for estimating the MFS, and OS. An interaction term between receipt of prior local therapy and treatment arm will be introduced in the multivariable Cox model to determine the effect modifying role of prior local therapy on response to apalutamide.

A similar approach will be used to determine the association of type of prior local therapy (radical prostatectomy vs. radiation therapy vs. both compared to no local therapy) with MFS and OS and also to determine its effect modifying role. Grambsch Therneau test will be applied to verify proportionality assumption. In presence of violation of proportionality weighted Cox regression models will be applied. A p-value <0.05 will be considered statistically significant.
Software Used:
RStudio
Project Timeline:

- Project submission: January 2023
- Contract: March 2023
- Analysis: April 2023 to October 2023
- Abstract Submission (GU ASCO 2024): October 2023
- Paper Draft circulation: October to December 2023
- Paper Submission: January 2024

Dissemination Plan:

- Abstract presentation in GU ASCO 2024

- Submission of manuscript first-quartile oncology journals: Journal of Clinical Oncology, European Urology, Annals of Oncology, International Journal of Radiation Oncology Biology, Physics.

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