

## 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](mailto: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:** M.B.B.S

**Primary Affiliation:** Department of Radiation Oncology, Rush University Medical Center, Chicago, IL, USA

**SCOPUS ID:**

**First Name:** Christopher J.D.

**Last name:** Wallis

**Degree:** M.D., PhD, FRCSC

**Primary Affiliation:** Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA

**SCOPUS ID:**

**First Name:** Scott C.

**Last name:** Morgan

**Degree:** M.D., MSc, FRCPC

**Primary Affiliation:** Radiation Medicine Program, The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada

**SCOPUS ID:**

**First Name:** Yilun

**Last name:** Sun

**Degree:** Phd, MA, BS

**Primary Affiliation:** University of Michigan

**SCOPUS ID:**

**First Name:** Daniel

**Last name:** Spratt

**Degree:** MD

**Primary Affiliation:** UH Seidman Cancer Center

**SCOPUS ID:**

**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\\_malone\\_2.pdf](https://yoda.yale.edu/system/files/coi_malone_2.pdf)

[https://yoda.yale.edu/system/files/yoda\\_coi\\_roy\\_2.pdf](https://yoda.yale.edu/system/files/yoda_coi_roy_2.pdf)

[https://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2019\\_wallis\\_2.pdf](https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_wallis_2.pdf)

[https://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2019\\_morgan\\_2.pdf](https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_morgan_2.pdf)

[https://yoda.yale.edu/system/files/yilun\\_sun\\_coi\\_0.pdf](https://yoda.yale.edu/system/files/yilun_sun_coi_0.pdf)

[https://yoda.yale.edu/system/files/dr\\_spratt\\_coi\\_0.pdf](https://yoda.yale.edu/system/files/dr_spratt_coi_0.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. [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

## Research Proposal

### Project Title

Association of Quality-of-Life Parameters with Survival Outcomes in High-Risk Metastatic Castrate Sensitive Prostate Cancer

### Narrative Summary:

There remains a lack of clarity on whether health related QoL parameters bear any association with survival outcomes in mCSPC. Our study aims to explore the association of QoL parameters at baseline with PFS and OS in high-risk mCSPC patients. The findings of our study might provide an additional rationale for the incorporation of QoL assessment into clinical trials exploring the benefit of newer systemic treatments and local therapies.

### Scientific Abstract:

#### Background:

Previous studies have shown a significant association of quality of life (QoL) parameters with overall survival (OS) and progression-free survival (PFS) in men with metastatic castrate resistant prostate cancer. However, it is unclear whether such an association exists for high-risk metastatic castrate sensitive prostate cancer (mCSPC).

#### Objective:

To evaluate the association of baseline QoL parameters with PFS and OS

#### Design and Participants:

Secondary analysis of LATITUDE trial with patients treated with ADT + abiraterone + prednisone or ADT + dual placebos and had baseline QoL parameters available

#### Main Outcome Measures:

PFS and OS

#### Statistical Analysis:

Cox proportional hazard models will be fitted to PFS and, separately, OS. We will include total score from FACT-G, FACT-P, prostate cancer subscale score (PCS), and FACT-P trial outcome index (TOI) score, and subdomains such as physical well-being (PWB), emotional well-being (EWB), functional well-being (FWB), and social/family well-being (SWB) scores. To minimize instability of the models resulting from high multicollinearity, separate models will

be fit for each of the following domains: FACT-P total score, FACT-G total score, FACT-P TOI, and FACT-P PCS. The remaining sub-domains will be introduced in a separate single model. Additional factors that will be included in the models are Gleason score, baseline PSA, race, region of study, ethnicity, presence of visceral/nodal/bone metastasis, number of bone metastases, site of visceral metastasis, treatment group, ECOG PS, and age.

### **Brief Project Background and Statement of Project Significance:**

#### **BACKGROUND**

There have been significant therapeutic advances in metastatic castrate sensitive prostate cancer (mCSPC) in the last few years. Four systemic agents including abiraterone acetate, enzalutamide, apalutamide, and docetaxel and local therapy in the form of prostate-directed radiotherapy have been shown to confer an overall survival advantage in men with mCSPC. (1–7) Additionally, the quality of life (QoL) analysis from the STAMPEDE study showed that global QoL was significantly higher in the first 2 years of treatment for patients treated with abiraterone compared to those treated with docetaxel. (7) However, this difference did not meet the threshold of clinical relevance.

The Prostate Cancer Clinical Trials Working Group 3 highlighted the need to optimize assessment and analysis of patient-reported outcome data and recommended evaluating the association between early changes in individual outcome measures (e.g., patient-reported outcomes) and later events such as PFS or OS. Although such associations have been explored in patients with mCRPC, no study to date has looked into this association in patients with mCSPC despite significant advancements in the management of this patient population. These exploratory analyses investigating the association between QoL and PFS and OS in the LATITUDE study at baseline will provide us clear information on such associations and will provide additional information to tailor treatment decisions for this patient population.

The LATITUDE study, which included patients with high-risk mCSPC, demonstrated the addition of abiraterone to androgen-deprivation therapy (ADT) conferred significant benefits in overall survival (OS) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76;  $P < 0.001$ ) and radiographic progression-free survival (rPFS) (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55;  $P < 0.0001$ ). (4, 8) Furthermore, median time to worst pain intensity progression, median time to worst fatigue intensity, and median time to deterioration of functional status was significantly superior in the abiraterone arm as compared to the placebo arm. (9) Despite level I evidence demonstrating significant survival advantages and QoL improvement, independently, with these systemic agents, it remains unclear if there is an association between baseline QoL parameters with survival outcome.

#### **STATEMENT OF SIGNIFICANCE**

The Prostate Cancer Clinical Trials Working Group 3 acknowledged the need to optimize assessment and analysis of patient-reported outcome (PRO) data and recommended evaluating the association between early changes in individual outcome measures (e.g., PROs) and later events such as radiographic progression-free survival (rPFS) or overall survival (OS). (10) In metastatic castration-resistant prostate cancer (mCRPC), improvement in QoL has been associated with improved clinical outcomes. (11) However, there remains uncertainty regarding the relationship between baseline QoL and survival outcomes.

We propose a secondary analysis of LATITUDE study to determine the association of baseline quality of life parameters with PFS and OS.

#### **Specific Aims of the Project:**

Primary Endpoint:

- To determine the association of baseline QoL parameters with PFS after adjusting for patient-related and clinical variables
- To determine the association of baseline QoL parameters with OS after adjusting for patient-related and clinical variables

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

Other

To evaluate association of baseline patient-reported outcomes with standard oncologic outcomes in advanced malignancies

#### **Research Methods**

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

Data source: LATITUDE trial dataset

Inclusion Criteria:

- Patients treated with ADT + abiraterone + prednisone or ADT + dual placebos in the LATITUDE trial
- Patients who have information on baseline QoL parameters including physical wellbeing, emotional wellbeing, functional wellbeing, and social/family wellbeing scores, FACT-G total score, FACT-P total score, prostate cancer subscale score (PCS), and FACT-P trial outcome index (TOI) score from FACT-P questionnaire.

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

- Progression-free survival as the time from randomization to the occurrence of radiographic progression, clinical progression, PSA progression or death from any cause. Radiographic and clinical progression will be defined according to the definitions established in the LATITUDE trial protocol. PSA progression will be defined as a 25% increase from the baseline value and 2 ng/ml absolute increase after 12 weeks of treatment initiation.
- Overall survival will be defined as the time from randomization to death from any cause.

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

- Physical wellbeing (PWB) score from FACT-P
- Emotional wellbeing (EWB) score from FACT-P
- Functional wellbeing (FWB) score from FACT-P
- Social/family wellbeing (SWB) scores from FACT-P
- FACT-G total score from FACT-P
- FACT-P total score from FACT-P
- Prostate cancer subscale score (PCS) from FACT-P
- FACT-P trial outcome index (TOI) score from FACT-P

## **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
- Ethnicity: Categorical
- Age, height, weight: Continuous
- Race: Categorical
- Region of study: Categorical
- Time from ADT treatment to trial treatment initiation: Continuous
- Presence of bone, node, and visceral metastases: yes/no: Categorical
- Site of visceral metastasis: Categorical
- Number of bone metastasis: Ordinal
- Gleason Score: Ordinal
- ECOG PS: Ordinal (0-2)

Baseline and Post-Baseline Variables:

- PSA: Continuous
- Time of radiographic progression
- Time of clinical progression
- Time of PSA progression
- Time of death
- Causes of death

## **Statistical Analysis Plan:**

Cox proportional hazard models with baseline QoL parameters will be fitted to time-to-event data (PFS and, separately, OS). PFS will be defined as the time from randomization to the occurrence of radiographic progression, clinical progression, PSA progression or death from any cause. Radiographic and clinical progression will be defined according to the definitions established in the LATITUDE trial protocol. PSA progression will be defined as a 25% increase from the baseline value and 2 ng/ml absolute increase after 12 weeks of treatment initiation. OS will be defined as the time from randomization to death from any cause. We will include QoL parameters such as

FACT-G total score, FACT-P total score, prostate cancer subscale score (PCS), and FACT-P trial outcome index (TOI) score. Additional QoL parameters will include physical well-being (PWB), emotional well-being (EWB), functional well-being (FWB), and social/family well-being (SWB) scores from FACT-P. Baseline clinical or patient-related variables such as Gleason score, baseline PSA, ethnicity, race, region of study, visceral metastasis (yes/no), bone metastasis (yes/no), nodal metastasis (yes/no), site of visceral metastasis, number of bone metastases, Eastern Cooperative Group performance status (ECOG PS) score, treatment regimen, and age will also be included in the models. To minimize instability of the final multivariate model potentially resulting from high multicollinearity, separate models will be fit for each of the following domains: FACT-P total score, FACT-G total score, FACT-P TOI, and FACT-P PCS. The remaining sub domains (PWB, FWB, SWB, and EWB) will be introduced in a separate single model and no other domains will be included in that model. Grambsch Therneau test will be used to test proportionality assumption. Although no formal adjustment of p-values will be done to address the multiplicity issue, we will interpret p-values conservatively.

Software Used:

RStudio

#### Project Timeline:

- Project submission: January 2021
- Contract: February-March 2021
- Analysis: April-October 2021
- Abstract Submission (ASCO GU 2022): October 2021
- Paper Draft circulation: January-February 2022
- Paper Submission: April-May 2022

#### Dissemination Plan:

- Abstract presentation in ASCO GU 2022
- Submission of manuscript first-quartile oncology journals: Journal of Clinical Oncology, Journal of National Comprehensive Cancer Network, European Urology, Annals of Oncology

#### Bibliography:

Reference:

1. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N. Engl. J. Med.* 2017;377:338–351.
2. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. [www.thelancet.com](http://www.thelancet.com). 2018;392.
3. Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N. Engl. J. Med.* 2015;373:737–746.
4. Fizazi K, Tran NP, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2019;20:686–700.
5. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N. Engl. J. Med.* 2019;381:121–131.
6. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet.* 2016;387:1163–1177.
7. Rush HL, Cook AD, Brawley CD, et al. Comparative quality of life in patients randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial. *J. Clin. Oncol.* 2020;38:14–14.
8. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N. Engl. J. Med.* 2017;377:352–360.
9. Chi KN, Protheroe A, Rodríguez-Antolín A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. *Lancet Oncol.* 2018;19:194–206.
10. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. *J. Clin. Oncol.* 2016;34:1402–1418.
11. Beer TM, Miller K, Tombal B, et al. The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant prostate cancer patients: Exploratory analyses of AFFIRM and PREVAIL studies. *Eur. J. Cancer.* 2017;87:21–29.

**Supplementary Material:**

[https://yoda.yale.edu/sites/default/files/idea2\\_-\\_correlation\\_of\\_health-related\\_quality\\_of\\_parameters\\_wtih\\_overall\\_survival\\_version\\_1.3\\_jan\\_13\\_2020.docx](https://yoda.yale.edu/sites/default/files/idea2_-_correlation_of_health-related_quality_of_parameters_wtih_overall_survival_version_1.3_jan_13_2020.docx)