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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_1.pdf
https://yoda.yale.edu/system/files/yoda_coi_roy_1.pdf
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https://yoda.yale.edu/system/files/dr._spratt_coi.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

Prognostic Indicators in High-Risk Metastatic Castrate Sensitive Prostate Cancer

Narrative Summary:

There is an unmet need for prognostic models that can predict risk of progression or death in patients with high-risk mCSPC. Additionally, it is unknown whether time to progression has an association with subsequent risk of death. Our study aims to address these two important aspects in men with high-risk mCSPC. We plan to build two prognostic models to predict the risk of progression or death and, separately and independently, the risk of death in this patient population and aim to explore the association of time to progression with risk of death. It is hoped that these models will help tailor treatment in these patients and in the design of future randomized trials evaluating new therapies

Scientific Abstract:

Background:
Despite significant advancement in the management of metastatic castrate sensitive prostate cancer (mCSPC), well-validated prognostic models that can predict for progression-free survival (PFS) and overall survival (OS) for this patient population is still lacking.
Objective:
Using readily available baseline clinical and laboratory data we aim to build independent prognostic models for PFS, and OS.
Design and Participants:
Secondary analysis with patients treated with ADT + abiraterone + prednisone or ADT + dual placebo in the LATITUDE trial
Main Outcome Measures:
PFS, and OS
Statistical Analysis:
Baseline clinical variables including Gleason score, ethnicity, race, region of study, presence of visceral

metastases, site of visceral metastases, presence of bone metastases, number of bone metastases, presence of lymph node metastases, Eastern Cooperative Group performance status, and age will be included in addition to treatment regimen and laboratory variables including baseline neutrophil:lymphocyte ratio, baseline platelet:lymphocyte ratio, baseline albumin, baseline lactate dehydrogenase, baseline PSA, alkaline phosphatase, and hemoglobin will be used to create the prognostic models for PFS and OS. Prognostic factors for PFS and OS will be identified by recursive partitioning analysis. Additionally, we plan to estimate the association of time to progression with risk of death using state arrival extended Markov proportional hazard model with adjustment for clinical variable and number of life-prolonging therapy received after progression.

Brief Project Background and Statement of Project Significance:

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) Although the CHAARTED definition of low-volume versus high-volume disease has often been used to stratify patients with mCSPC, (8) models that can yield prognostic information in mCSPC are lacking, especially in the high-risk mCSPC subpopulation. The only model that exists for mCSPC cohort is the Glass model which was validated in GETUG-15 study, a more heterogenous population. (9, 10) Further, the GETUG-15 trial failed to demonstrate a benefit to intensified therapy in mCSPC, in contrast to nearly every other trial (including LATITUDE) in this disease space. Thus, there remains an important unmet clinical need for a prognostic model that predicts PFS and OS among patients with high-risk mCSPC.
LATITUDE is a phase III randomized study in which patients with high-risk mCSPC (defined as 2 or more of the following: at least 3 bony lesions, visceral metastasis, and Gleason score 8-10) were randomly allocated to receive either androgen deprivation therapy plus abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) (the abiraterone group) or androgen deprivation therapy plus dual placebos (the placebo group). (1, 11) The addition of abiraterone to androgen deprivation therapy (ADT) conferred a significant overall survival (OS) benefit (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; P<0.001) and significant radiographic progression-free survival (rPFS) benefit (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; P<0.0001).
We propose a secondary analysis of the LATITUDE study to build independent prognostic models to predict PFS and OS in patients with high-risk mCSPC treated with ADT alone or ADT and abiraterone combination. Additionally, we also plan to estimate the association of time to radiographic, clinical or PSA progression with risk of overall mortality.

Significance:
Our prognostic models will serve as an essential tool to predict clinically significant outcomes in men with high-risk mCSPC, which in turn can be used to optimize the use of systemic and/or local treatments for this patient population in routine clinical practice. We would also envision that these models would inform the design of future clinical trials in mCSPC.

Specific Aims of the Project:

Primary Endpoint:
- To build independent models for prediction of PFS and OS to stratify patients with high-risk mCSPC into different prognostic groups based on the risk of progression or death and separately based on the risk of death.
Secondary Endpoint:
- To estimate the association of time to radiographic, clinical or PSA progression with risk of overall mortality.

What is the purpose of the analysis being proposed? Please select all that apply.
Research on clinical prediction or risk prediction

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 placebo in the LATITUDE trial

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

- Overall survival will be defined as the time from randomization to death from any cause
- 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.

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

Baseline Factors:
- Treatment arm: Categorical
- Ethnicity: Categorical
- Race: Categorical
- Region of study: Categorical
- Age, height, weight: Continuous
- Presence of bone, node, and visceral metastases: yes/no (categorical)
- Site of visceral metastasis: Categorical
- Number of bone metastasis: Ordinal
- Gleason Score: Ordinal
- Prior surgery or radiation therapy to primary: yes/no
- ECOG PS: Ordinal (0-2)
- Date of randomization (date format) – to calculate PFS and OS
- Time from ADT to trial treatment start in months

Baseline and Post-Baseline Variables:
- PSA: Continuous
- Hemoglobin: Continuous
- Serum albumin: Continuous
- Serum alkaline phosphatase: Continuous
- Serum LDH: Continuous
- Total WBC count with differential counts
- Platelet count
- Post-baseline radiographic evaluation (BS/CT scan): categorical
- Time of radiographic progression (date format) – to calculate PFS
- Time of clinical progression (date format) – to calculate PFS
- Time of PSA progression (date format) – to calculate PFS
- Time of death (date format) – to calculate OS
- Cause of death
- Life prolonging therapy received after progression – (Yes/no) and its details

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

None

Statistical Analysis Plan:

Separate models will be created for PFS and OS. Baseline clinical variables including Gleason score, ethnicity, race, region of study, presence/absence of visceral metastasis, presence/absence of bone metastasis, site of visceral metastasis, presence/absence of lymph node metastasis, number of skeletal metastasis, Eastern Cooperative Group performance status (ECOG PS) score, and age will be included in addition to treatment regimen and laboratory variables including baseline neutrophil:lymphocyte ratio, baseline platelet:lymphocyte ratio, baseline albumin, baseline lactate dehydrogenase (LDH), baseline prostate-specific antigen (PSA), baseline alkaline phosphatase (ALP), and baseline hemoglobin (Hb). To validate the predictive significance of prognostic groups in this analysis, the complete data set will be divided into test (2/3rd) and validation sets (1/3rd). We will use recursive partitioning as a method of modeling predictors in the form of a regression or decision tree. Recursive partitioning evaluates all possible dichotomous splits on all prognostic factors included in the model and then chooses the split providing the greatest separation of the 2 groups with respect to progression-free survival and overall survival, respectively. These will be evaluated with the log rank statistics. The process will continue until the

complete data set is grown and there are many nodes or groups with only a few patients per group. Tree pruning methods described by LeBlanc and Crowley will be implemented to select the best pruned tree. The terminal nodes from separate branches of the tree will be combined or amalgamated to form final prognostic groups. This approach will create regression trees that classify patients into prognostic groups based on survival outcome. The definition of these prognostic groups will be applied to the validation data set to validate the models.

To evaluate the association of time to progression with OS, we will apply a state arrival extended Markov proportional hazard model. A three-state model will be generated consisting of pre-treatment baseline state, a state of progression and a state of death. To distinguish transition to the “death” state from the baseline state or progression state, a time-dependent covariable, indicating whether progression has occurred or not, will be introduced. For transition from the baseline state, the value of this covariable will be equaled 0 if the death state will be entered directly; for patients transitioning through the progression state, the value of this covariable will be equaled 1 because the death state will be entered from the progression state. As time to progression is important only for transition from progression to death, we will include time to progression for this transition i.e. progression?death. Similarly, number of life-prolonging treatment modalities received after progression will be also included for this transition. Additional transition specific variables will be comprised of age, performance status at baseline, pre-treatment PSA, treatment regimen, Gleason score, presence of visceral, nodal, or skeletal metastasis, ethnicity, number of skeletal metastasis, and site of visceral metastasis. Grambsch-Therneau test will be used to assess for proportionality assumption.
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:

1. 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.
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. 2018;392.
3. 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.
4. 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.
5. 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.
6. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N. Engl. J. Med. 2019;381:13–24.
7. 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.
8. 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.
9. Gravis G, Boher JM, Joly F, et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur. Urol. 2016;70:256–262.
10. Glass TR, Tangen CM, Crawford ED, et al. Metastatic carcinoma of the prostate: Identifying prognostic groups

using recursive partitioning. J. Urol. 2003;169:164–169.
11. 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.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/idea1_-_prognostic_indicators_from_latitude_study_-_version_1.3_january_13_2020_4.docx