

Principal Investigator

First Name: Antonio
Last Name: Finelli
Degree: MD, MSc, FRCSC
Primary Affiliation: Princess Margaret Cancer Centre
E-mail: antonio.finelli@uhn.ca
Phone number: 416-946-4501 x2851
Address: 610 University Ave.
3-130,
City: Toronto
State or Province: Ontario
Zip or Postal Code: M5G 2M9
Country: Canada

General Information

Key Personnel (in addition to PI):

First Name: Lisa
Last name: Martin
Degree: PhD
Primary Affiliation: Princess Margaret Cancer Centre
SCOPUS ID:

First Name: Maria
Last name: Komisarenko
Degree: MSc
Primary Affiliation: Princess Margaret Cancer Centre
SCOPUS ID:

First Name: Shabbir
Last name: Alibhai
Degree: MSc, MD, FRCPC
Primary Affiliation: Toronto General Research Institute
SCOPUS ID:

First Name: Jaime
Last name: Herrera Caceres
Degree: MD
Primary Affiliation: Princess Margaret Cancer Centre - University Health Network
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?: Data Holder (Company)

Conflict of Interest

http://yoda.yale.edu/system/files/finelli-yoda_project_coi_form_for_data_requestors_2016novsigned.pdf

http://yoda.yale.edu/system/files/alibhai-signedcoijune2016_0.pdf

http://yoda.yale.edu/system/files/komisarenko-yoda_project_coi_form_for_data_requestors_2016novsigned_0.pdf

http://yoda.yale.edu/system/files/martin-yoda_project_coi_form_for_data_requestors_2016novsigned.pdf

http://yoda.yale.edu/system/files/herrera_caceres-yoda_project_coi_form_signed.docx.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

Associated Trial(s):

1. [NCT00887198 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic 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

Predictors of radiographic progression in metastatic castration-resistant prostate cancer: Retrospective analysis of COU-AA-302

Narrative Summary:

Men with prostate cancer that has spread to other organs (metastatic) are monitored by bone scans and other imaging to see if the cancer continues to grow or spread (progression). If progression is seen, cancer treatment may be changed or stopped. The optimal frequency of imaging for monitoring these patients is not known.

The objective of this project is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify characteristics of patients and/or their cancer that predict when cancer is progressing. This information may be used to tailor the frequency of imaging based on such characteristics and lead to better utilization of imaging.

Scientific Abstract:

Background: Imaging is used for ongoing surveillance of disease progression for mCRPC patients to make decisions about treatment (for example, stopping or changing drug treatments). However, imaging, particularly CT scans and MRIs, is costly and access is limited. The optimal frequency of imaging for mCRPC patients is not known.

Objective: The objective of this work is to identify predictors of radiographic progression in men with mCRPC with the goal of modifying the frequency of imaging based on patient and/or disease characteristics. Ultimately, this work will lead to better utilization of imaging.

Study Design: Retrospective cohort study.

Participants: mCRPC patients from COU-AA-302 treated with abiraterone or placebo and had not received previous chemotherapy.

Main Outcome Measures(s): Time to radiographic progression defined as the time from randomization to the disease progression in bone or soft tissue.

Statistical Analysis: We will use multivariable Cox proportional hazards modelling to assess the association of covariates with time to progression. We will first include all baseline covariates and use a manual backward selection of statistically significant variables. The number of variables in the model may be reduced based on lack of effect on the c-index. Time-dependent covariates including PSA response, patient-reported outcomes and adverse effects will then be added and their contribution assessed with partial log likelihood test and c-index. The analysis will be performed in all subjects and separately in the abiraterone and placebo groups.

Brief Project Background and Statement of Project Significance:

PLEASE NOTE: This request is virtually identical to our previous approved request (YODA number 2016-0979) for data from COU-AA-301.

About 90% of advanced prostate cancer patients develop bone metastases and serial bones scans are commonly used to identify progression to metastatic disease. In metastatic castrate-resistant prostate cancer (mCRPC), the goal of imaging is to monitor further progression of disease to make decisions about treatment options (for example, stopping or changing drug treatments). Changes in existing bone metastases are not easily or reliably measured; therefore, the appearance of new bone metastases (after ruling out bone flare) is used to assess progression in bone [1]. CT or MRI scans can be used to detect new metastases in soft tissue (nodes and visceral) and to measure changes in soft tissue metastases using modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria

In a clinical trial (COU-AA-302) of mCRPC patients being treated with abiraterone (or placebo) prior to chemotherapy, approximately 40% of men progressed in bone only, 40% progressed in soft tissue only, and 12% progressed in both bone and soft tissue [2, 3]. Only 6% of men died before evidence of progression. These results suggest that both bone scans and CT or MRI scans are needed to ensure that evidence of progression is detected. In this trial, radiographic progression of disease occurred on average around 14 to 16 months from treatment initiation, but the timing of progression was variable between men; with some men progressing by only 8 to 12 weeks [2]. The optimal schedule of imaging for mCRPC patients is not known and may differ depending on patient and disease characteristics.

Statement of Project Significance

Imaging, particularly CT and MRI, is costly and access is limited. Ongoing surveillance of disease progression is needed for mCRPC patients; however, the optimal frequency of imaging in terms of effectiveness and cost is not known. The goal of the proposed work is to identify predictors of radiographic progression in men with mCRPC. These factors may be used to determine the appropriate/optimal monitoring schedule for subgroups of patients based on their characteristics and lead to better utilization of imaging.

Based on studies of factors associated with overall survival in mCRPC patients [4-6], we hypothesize that several clinically available baseline patient and tumour characteristics will be associated with time to radiographic progression (see list of variables below). Changes in PSA levels and patient reported outcomes and/or the occurrence of adverse effects may also predict time to radiographic progression.

Data on time to disease progression is highly dependent on the schedule of assessments [4]. Therefore, data from clinical trials, where imaging is scheduled at standard intervals in all patients, are necessary for this type of analysis.

Specific Aims of the Project:

Overall Objective: To identify predictors of radiographic progression in men with mCRPC to facilitate better utilization of imaging in the follow-up of these patients.

Aim 1: To examine the association of clinically available baseline factors with radiographic progression (all subjects and stratified by treatment group).

Aim 2: To examine the association of clinically available baseline factors with radiographic progression in bone and soft tissue separately.

Aim 3: To examine whether changes in PSA, patient reported pain and/or the occurrence of adverse effects are associated with radiographic progression, independent of baseline variables.

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

Other

To identify predictors of radiographic progression in men with mCRPC to facilitate better utilization of imaging in the follow-up of these patients.

Research Methods

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

The data source is COU-AA-302. All subjects included in the COU-AA-302 trial will be included in the proposed work.

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

The main outcome measure is time to radiographic progression defined as time from baseline to occurrence of tumor progression in bone or soft tissue, or death.

The COU-AA-302 protocol included CT, MR and bone scans at baseline and every 8 weeks during the first 24 weeks and every 12 weeks thereafter.

Radiographic progression was determined by at least one of the following (as defined in original trial protocol):

Bone: Progression on bone scans with ≥ 2 new lesions not consistent with tumor flare

Soft Tissue: Progression by CT or magnetic resonance imaging was defined as a ≥ 20% increase from nadir in target lesion sum of long diameters, appearance of new soft tissue or visceral lesions, and/or unequivocal progression of baseline nontarget lesions.

Patients who did not show progression and were alive at last follow-up will be censored at that time. Patients with no baseline assessment will be censored at randomization.

The following variables are needed to calculate time to progression:

Time from baseline to radiographic progression or last follow-up

Type of radiographic progression (bone or soft tissue or death)

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

There is not one main predictor variable for the proposed work. We will assess the association of various factors with time to radiographic progression (see Table below). While we recognize that multiple testing may be an issue when examining several variables, we note that most of the variables in the table have been shown to be associated with overall survival (OS) for mCRPC [4-6]; therefore, we hypothesize a priori that they will be associated with time to radiographic progression. Radiographic was strongly positively associated with OS in COU-AA-302 n [2].

Baseline:

- 1 Treatment Arm (Abiraterone or placebo)
- 2 Age at entry (continuous)
- 3 Height (continuous)
- 4 Weight (continuous)
- 5 Ethnicity
- 6 ECOG Performance Status* (Categorical:0, 1, 2)
- 7 Type of disease progression at baseline (PSA only/radiographic/or both)
- 8 Presence of liver metastases* (Present/Absent)
- 9 Presence of bone metastases (Present/absent)
- 10 Presence of nodal metastases (Present/absent)
- 11 Presence of visceral metastases (Present/absent)
- 12 Time from diagnoses to start of abiraterone
- 13 Time from start of initial LHRH agonist therapy to abiraterone treatment* (continuous)

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

- 14 Albumin* (continuous)
- 15 Alkaline Phosphatase* (continuous)
- 16 Lactate Dehydrogenase* (continuous)
- 17 Gleason Score (Ordinal)
- 18 Hemoglobin (continuous)

19 Presence of Pain (BPI-SF item 3) (ordinal)

20 Baseline PSA (continuous)

21 Prior radiation therapy (Yes/No)

22 Prior prostatectomy (Yes/no)

* reported as prognostic for overall survival in COU-AA-301 in ref. 5 and 6

Note: Continuous variables may be categorized after data examination.

Post baseline

PSA PSA progression (Yes/no)

Time to PSA progression (continuous)

PSA level at each visit (continuous)

Pain Presence of Pain (BPI-SF item 3) at each visit (Ordinal)

Analgesic score at each visit (0 = none, 1 for non-opioid analgesics, 2 for opioids for moderate pain, and 3 for opioids for severe pain)

Statistical Analysis Plan:

All analyses will be stratified by treatment group (abiraterone vs placebo) because predictors of progression may differ by treatment.

The distribution of baseline characteristics and outcome measures will be examined by descriptive statistics and graphically using histograms. Transformations will be applied as appropriate.

Univariate: We will plot Kaplan Meier curves of survivorship functions for all categorical variables and for categories of continuous variables. The hazard ratio (HR) and 95% confidence intervals (CI) will be estimated using the Cox proportional hazards (PH) model.

Multivariate: We will use multivariable Cox PH modeling to assess the independent association of covariates with time to progression. We will first include all baseline covariates (Table 1) and use a manual backward selection of statistically significant variables ($P < 0.05$). We may reduce the number of variables in the model based on their lack of effect on overall concordance (C-index) of the model, for reasons of parsimony. Time dependent variables for PSA, pain and adverse effects will be added to the baseline model and their contribution assessed tested with partial log likelihood test and change in the C-index.

The validity of the PH assumption will be checked by testing interactions between time and each variable in the models and by plotting $\ln(\text{survival})$ vs $\ln(\text{time})$ to check for parallel lines. Continuous variables will be dichotomized to graphically assess the PH assumption. All statistical analyses will be performed using the Statistical Analysis System (version 9; SAS Institute, Cary, NC).

Sample Size/Power: The statistical power depends on the number of events of progression. According to Morris 2015 (COU-AA-302, ref 2), there were a total of 607 events of progression (271 abiraterone group and 333 in control). We plan to examine a maximum of about 25 variables (see list above) which gives us about 24 events per variable (higher than the guideline of 10 events per predictor variable in a model). In the abiraterone group, we would have 11 events per variable and in the placebo group we would have 13 events per variable.

Project Timeline:

1. Completion of Contract: December 2016
2. Obtain dataset: January 2017
3. Analysis: February to April 2016
4. Submit report to YODA: May 2017
5. Circulate Abstract for ASCO June 2017
6. Circulate paper July 2017

Dissemination Plan:

Abstract presentation for ASCO 2018

Paper – potential journals – Clinical Cancer Research, European Urology, Annals of Oncology

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3. Armstrong AJ, Halabi S: Making progress on progression in metastatic prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015, 33(12):1322-1324.
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5. Ravi P, Mateo J, Lorente D, Zafeiriou Z, Altavilla A, Ferraldeschi R, Sideris S, Grist E, Smith A, Wong S et al: External validation of a prognostic model predicting overall survival in metastatic castrate-resistant prostate cancer patients treated with abiraterone. *European urology* 2014, 66(1):8-11.
6. Halabi S, Lin CY, Kelly WK, Fizazi KS, Moul JW, Kaplan EB, Morris MJ, Small EJ: Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014, 32(7):671-677.