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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Cancer Council SA
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_ahmad_abuhelwa_1.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_ashley_hopkins_1.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_michael_sorich_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. NCT00638690 - COU-AA-301 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
2. NCT00887198 - COU-AA-302 - 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
3. NCT01695135 - ABI-PRO-3001 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
4. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant Prostate Cancer
5. NCT01867710 - 212082PCR2023 - A Randomized Phase 2 Study Evaluating Abiraterone Acetate With Different Steroid Regimens for Preventing Symptoms Associated With Mineralocorticoid Excess in Asymptomatic, Chemotherapy-naïve and Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients
6. 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

Predictors of therapeutic and adverse effects of medicines used in the treatment of prostate cancer

Narrative Summary:

Prostate cancer is the second most commonly diagnosed cancer worldwide. For example, in 2018 it is expected that nearly 1.3 million new cases and about 360,000 deaths will be resultant of the disease [1]. There are many important medicines used in the treatment of prostate cancer, however, response and toxicity to these therapies can be highly unpredictable. Thus, more research is required to develop clinical tools that enable improved prediction of therapeutic and adverse outcomes for patients using prostate cancer medicines. This may enable patients and clinicians to make better decisions regarding whether to commence, continue, discontinue or change dosing of prostate cancer medicines.

Scientific Abstract:

Background: Abiraterone acetate is an important treatment option for prostate cancer. However, response and toxicity to abiraterone acetate can be highly variable between patients.

Objectives: To develop predictive models of therapeutic and adverse effect outcomes in patients using abiraterone acetate to treat prostate cancer. Being able to identify the profile of expected therapeutic and adverse effect outcomes may enable patients and clinicians to make better decisions regarding whether to commence, continue, discontinue or change dosing of abiraterone acetate.

Study design: A pooled observational cohort design will be used to conduct a meta-analysis of transparently shared clinical trials data.

Participants: Prostate cancer patients treated with abiraterone acetate or relevant comparator arms

Main Outcome Measure(s): the measures of the therapeutic response (best overall response based on response evaluation criteria in solid tumours (RECIST), duration of response, progression, overall and progression-free survival).
Statistical analysis: Cox-proportional hazard/time-to-event models will be used to assess the association between potential predictors and the time to an adverse effect or response/progression/survival. The association of potential predictors with binary outcomes will be modelled using logistic regression. Longitudinal analysis will be used to assess the patterns of longitudinal changes of key continuous variables.

Brief Project Background and Statement of Project Significance:

There are many important medicines used in the treatment of prostate cancer. However, response and toxicity to many therapies is highly unpredictable. For example, many eligible patients may not respond adequately to abiraterone acetate therapy when used in the treatment of advanced prostate cancer. Thus, more research is required to confirm and explore novel predictive markers of therapeutic and adverse effects of abiraterone acetate used in the treatment of prostate cancer.

This project seeks to enable improved prediction of the therapeutic and adverse outcomes of patients using medicines for the treatment of prostate cancer. This project with abiraterone acetate data is part of a bigger project submitted to Vivli (Vivli Project ID: 00005289) where available data from various prostate cancer patients treated with relevant contemporary treatment options will be meta-analysed to identify and validate predictors of the most important adverse effects, and clinical/biological/patient predictors of therapeutic outcomes such as response, tumor shrinkage, progression free survival (PFS) and survival.

Ultimately developing clinical prediction models for medicines in prostate cancer patients could be used to make informed decisions as to whether to commence, continue, discontinue or change dosing of these medicines which can eventually lead to improved health outcomes and significant cost savings.

Specific Aims of the Project:

Hypothesis:
Accessing transparently shared trial data on contemporary treatment options will facilitate the development of clinical prediction models capable of providing personalised likelihoods of the expected therapeutic and adverse outcomes of medicines used in the treatment of prostate cancer. Effective communication of personalised and well-validated predictions of an individual’s expected benefits and harms from therapy will improve shared decision making, lead to more informed and empowered patients, and enable patients and clinicians to make better decisions regarding whether to commence and continue medicines.

Specific Aims:
1. Identify baseline and on-treatment predictors and develop clinical prediction models of the key adverse effects of medicines used in the treatment of prostate cancer.
2. Identify baseline and on-treatment predictors and develop clinical prediction models of the key therapeutic outcomes (response, progression and survival) of medicines used in the treatment of prostate cancer.
3. Evaluate the heterogeneity of treatment adverse effects and therapeutic outcomes according to model predicted risk.

Research Methods

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

To precisely and validly determine the relationship between potential predictors and outcomes of interest it is important to have the maximum sample size possible across a range of different study populations and medicines (an increased number of studies increases the population diversity, and is thus more comparable to standard...
clinical practice). Therefore, all studies collecting baseline and follow-up clinical characteristic data, as well as adverse event or therapeutic outcome data for patients treated with medicines contemporarily used in the treatment of prostate cancer have been selected (model building will use the per-protocol populations). Data from relevant comparator arms will be required to understand the heterogeneity in treatment effect according to identified risk factors (analyses of the heterogeneity of treatment effects will use the intent-to-treat populations), and whether the risk factors identified are specific to a single medicine or are common across multiple therapies.

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

Data for main outcome measures including response (early, depth, best overall), overall survival, progression-free survival, adverse event outcomes (clinician / patient reported adverse effects that have been defined according to the international common toxicity criteria, and adverse events requiring medication changes), and drug exposure (concentration). The most recent in scope data cuts of these variables are required.

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

As most of the data commonly collected within a clinical trial contains some information on the immune system, disease severity and prognosis, toxicity risk or drug exposure, it is important to have access to all the baseline and follow-up clinical/biological/patient characteristic data collected on an individual for any given study. Covariates to be explored include, but not limited to:

- Baseline values. defined as the value closest and prior to the first dose of study treatment. Variables include:
  - Basic patient characteristics – e.g. age, sex, race / ethnicity, body mass index (BMI), weight, weight loss prior to diagnosis and therapy initiation, alcohol consumption, family history of disorders, and measures of performance status
  - Laboratory data - e.g. levels of lactate dehydrogenase (LDH), alkaline phosphatase, albumin, bilirubin, leucocyte and leucocyte subtype counts (e.g. WBC, lymphocyte, monocyte or eosinophils, neutrophil to lymphocyte ratio (NLR), haemoglobin, platelets, glucose, HBA1C, creatinine, C-reactive protein, circulating tumour cells, calcium, total protein, total triglycerides, cholesterol, blood urea nitrogen, and anaemia.

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

- Disease classification data - e.g. tumour stage and grade, site and histology/subtype of primary tumour, prior therapy, time to response / progression for previous therapies, sum of longest tumour diameter, time since diagnosis, number and sites of metastases, mutation and expression status of disease specific oncogenes, pathological features of tumour cells, cancer antigen levels
- Other common predictors – e.g. concomitant medications, respiratory comorbidity (e.g. asthma and COPD), other comorbid diseases (e.g. peripheral vascular disease, cerebrovascular disease, diabetes), simplified comorbidity score, organ dysfunction (e.g. liver, lung or renal), and other clinical, biological, vital statistics, laboratory, imaging, pharmacokinetic and patient-reported outcomes measures.
- Post-baseline values. Variables include time-varying clinical (e.g. adverse events such as rash), radiological (e.g. tumour size and spread), biological/laboratory (e.g. liver function markers, drug concentrations), vital statistics (e.g. weight, heart rate), disease classification, performance status, and other common time-dependent predictor data. Most recent data cuts of these variables are required

Statistical Analysis Plan:

The analysis for this project will be completed on Vivli platform. Other studies requested from vivli include: NCT02003924, NCT01664923, NCT01995513, NCT00974311, NCT01212991, NCT02236637, NCT00988208, NCT00672282, NCT00626548, NCT00617699, NCT00554229, NCT00519285, NCT00417079.

Cox-proportional hazard/time-to-event models will be used to assess the association between potential predictors and time to an adverse effect or survival. Associations will be reported as hazard ratios with 95% confidence intervals (CI). The association of potential predictors with binary outcomes (e.g. best overall response) will be modelled using logistic regression and will be reported as odds ratios with 95% CI. Time-dependent analyses will be used to assess the nature and patterns of longitudinal changes of key continuous variables (e.g. neutrophil counts). Standard meta-analysis methods will be employed to conduct cross platform pooling of identified associations (HR and OR pooling) in prostate cancer patients treated with contemporary treatment options with transparently shared data. The R Software will be used for data analysis.

Potential predictors will be prioritised according to biological/clinical plausibility and prior evidence of association.
with the relevant outcome (adverse events, therapeutic response, drug exposure). Should multiple values of a covariate be recorded multiple times for a single visit, the mean of the multiple reads taken at each visit will be used. Crude associations will be reported based on univariate analysis (adjusting only for the clinical trial and where appropriate the cancer medicine), and adjusted associations based on a multivariable analysis. Continuous variables will be assessed for non-linear associations with outcome. Clinical prediction models will be developed using multivariable analysis and will generally include all available known baseline predictors of the outcome of interest as well as covariates identified in univariate analysis. Penalised models will be used to minimise risk of overfitting. Early markers of exposure, response and toxicity will be primarily evaluated using a landmark approach where possible, with sensitivity analyses based on the use of time-dependent covariates. Landmark time will be dependent on the time points available in individual studies, and the time frame of changes in each specific predictor variable. As this analysis is primarily hypothesis generating and will require subsequent validation of any findings, no formal adjustment for multiple testing is intended. However, this limitation will be clearly stated in any publications of results. As it is expected that < 5% of data will be missing for any variable a complete case analysis is planned. Should variables with substantial missing data be present, the pattern and likely cause of the missing data will be evaluated and if missing at random is reasonable to assume then single regression imputation will be undertaken.

Analyses will also include evaluating the heterogeneity in toxicity incidence and response profiles according to model risk, as well as evaluating the predictors of the main adverse effects and response profiles for the medicines used in relevant comparator arms. Such analyses will allow a better understanding of the benefits of specific therapies, and whether the relationships identified are medicine specific or are common to multiple therapies. Predictors that have a clinically meaningful effect on mortality and adverse effects will be of primary interest. Based upon a 30% incidence of toxicity, a sample size of ~600 is required to detect a predictor (with a 10% frequency within the population) associated with a two-fold risk (?=0.05 with 80% power). Based upon an event rate of 40% during trial follow-up (e.g. for progression), ~450 participants are required for 80% power to detect a predictor (with 10% frequency within the population) associated with a two-fold hazard of the event (?=0.05).

**Software Used:**

R

**Project Timeline:**

The project is expected to take 1 year from the date of data access. Estimated start date 1 October 2020 with all analysis completed by 30 September 2021. Manuscripts will be drafted and submitted at each stage of the proposed project and will be shared with the YODA project at the time of submission.

**Dissemination Plan:**

Results of all completed analyses will be published in peer-reviewed international publications and where possible also presented at scientific meetings. Manuscript(s) will be targeted primarily to international oncology journals (e.g. BMJ oncology) and will be submitted as soon as possible following completion of the requisite analyses.

**Bibliography:**