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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_2022_ahmad_abuhelwa_signed_0.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_2022_ashley_hopkins_signed.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_2022_michael_sorich_signed.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. [NCT01722487 - PCYC-1115-CA - Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma](#)

2. [NCT01236391 - PCYC-1104-CA - Multicenter Phase 2 Study of Bruton's Tyrosine Kinase \(Btk\) Inhibitor, PCI-32765, in Relapsed or Refractory Mantle Cell Lymphoma](#)
3. [NCT01105247 - PCYC-1102-CA - A Phase 1b/2 Fixed-dose Study of Bruton's Tyrosine Kinase \(Btk\) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia](#)
4. [NCT01578707 - PCYC-1112-CA - A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase \(BTK\) Inhibitor Ibrutinib \(PCI-32765\) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma](#)
5. [NCT01611090 - PCI-32765CLL3001 - Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase \(BTK\) Inhibitor, in Combination With Bendamustine and Rituximab \(BR\) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma](#)
6. [NCT02165397 - PCYC-1127-CA - iNNOVATE Study: A Randomized, Double-Blind, Placebo- Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination With Rituximab in Subjects With Waldenström's Macroglobulinemia](#)
7. [NCT02264574 - PCYC-1130-CA - A Randomized, Multi-center, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Subjects With Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma](#)

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 exposure, therapeutic and adverse effects of ibrutinib used in the treatment of B-cell lymphomas

Narrative Summary:

Ibrutinib is a Bruton tyrosine kinases inhibitor (BTKI) and plays an important role in the treatment of B-cell lymphomas including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphomas (SLL) [1]. However, response and toxicity to ibrutinib can be highly variable and there are no accurate and reliable tools to date to accurately predict patients who will benefit most [2]. Using the diverse range of data from clinical trials, it is possible to identify predictors and develop clinical tools that enable improved prediction of their therapeutic and toxicity outcomes and inform treatment decisions.

Scientific Abstract:

Background: Lymphomas are 'blood cancers' in the lymph nodes. B-cell lymphomas include both Hodgkin's and non-Hodgkin's lymphomas. Ibrutinib is a Bruton tyrosine kinases inhibitor (BTKI) and plays an important role in the treatment of B-cell lymphomas including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphomas (SLL). However, response and toxicity to ibrutinib can be highly unpredictable.

Objectives: To identify predictors and develop predictive models of therapeutic and adverse effect outcomes of ibrutinib used to treat B-cell lymphomas. Being able to identify the expected response and adverse effect profile may enable patients and clinicians to make better decisions regarding whether to commence, continue or change the dosing of ibrutinib in patients with B cell lymphomas.

Study design: An observational cohort analysis of clinical trials individual-participant data.

Participants: Patients with B-cell lymphomas treated with ibrutinib or relevant comparator arms

Main Outcome Measure(s): 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 exposure data

(number of completed cycles, concentration).

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 survival time. 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% confidence intervals. Longitudinal analysis (e.g., linear, and non-linear mixed effect modelling) will be used to assess the nature and patterns of longitudinal changes of key continuous variables (e.g., drug concentration, neutrophil counts).

Crude associations will be reported based on univariate analysis (adjusting only for the study population and treatment arm), and adjusted associations based on multivariable analysis. Continuous variables will be assessed for non-linearity of association with outcomes using restricted cubic splines. Should multiple values of an assessed covariate be recorded for a single visit (e.g. blood pressure) the mean of the multiple reads will be used. The varying performance of clinical prediction models developed using multivariable analysis techniques including stepwise regressions, penalised methods [which minimise the risk of overfitting (e.g., elastic net analysis)], and machine learning [which excel in optimising prediction with high-dimensional data (e.g., random forest and gradient boosted methods)] will be assessed. Early markers of exposure, response and toxicity will be 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.

Analyses will include evaluating the heterogeneity in outcome predictors for B-cell lymphoma drugs as compared to relevant comparator. Such evaluations will allow a better understanding of whether the relationships identified are specific to a specific B-cell lymphoma drug or are common to standard treatment (i.e., common prognostic factors).

Brief Project Background and Statement of Project Significance:

There are many important medicines used in the treatment of B-cell lymphomas including ibrutinib. However, response and toxicity to ibrutinib is highly unpredictable. For example, many patients who initiate ibrutinib therapy do not respond to therapy and experience serious toxicity. Thus, more research is required to confirm and explore novel predictive markers of therapeutic and adverse effects of ibrutinib used in the treatment of B-cell lymphomas.

This project seeks to identify the most important predictors of the therapeutic and adverse outcomes of patients using ibrutinib for the treatment of B-cell lymphomas. This project was also submitted to Vivli (Vivli Project ID: 8567) to be able to access data packages through Vivli research environment.

Ultimately developing clinical prediction models for medicines used to treat B-cell lymphomas will enable patients and clinicians to make informed shared treatment decisions as to whether to commence, continue, discontinue or change dosing of ibrutinib which can eventually lead to improved health outcomes and significant cost savings.

Specific Aims of the Project:

The hypothesis of this project is that clinical predictors of response and adverse effects of B-cell lymphoma drugs can be developed from clinical trial data to enable informed decisions by patients and clinicians.

Specific aims:

1. Identify baseline and on-treatment predictors and develop clinical prediction models of the key therapeutic outcomes (response, progression and survival) of ibrutinib used in the treatment of B-cell lymphomas.
2. Identify baseline and on-treatment predictors and develop clinical prediction models of the key adverse effects of ibrutinib used in the treatment of B-cell lymphomas.
3. Evaluate the heterogeneity of treatment and adverse effect predictors for ibrutinib versus comparator therapies.

These analyses are primarily hypothesis generating and they will require subsequent validation.

What is your Study Design?:

Other

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

Other

identify predictors of therapeutic and toxicity outcomes

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 (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 cancer patients treated with ibrutinib have been selected (model building will use the per-protocol populations). Data from the comparator arms will be required to understand the heterogeneity in predictors between primary and comparator treatments (analyses of the heterogeneity of treatment effects will use the intent-to-treat populations).

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

Data for main outcome measures include 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 exposure data (number of completed cycles, 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:

Access to individual baseline and follow-up clinical/biological/patient characteristic data for a given study is important. Predictors to be explored include, but not limited to:

- Basic patient characteristics: e.g. age, sex, race, body mass index (BMI), weight, weight loss, smoking status, alcohol consumption, and measures of performance status
- Laboratory data - e.g. levels of lactate dehydrogenase, alkaline phosphatase, albumin, bilirubin, leucocyte and leucocyte subtype counts, haemoglobin, platelets, C-reactive protein.
- Patient-reported outcomes: e.g. patient-reported physical function, fatigue, global health, emotional function.
- Concomitant medications: e.g. antibiotics, acid antisecretory drugs (e.g. proton pump inhibitors), antihypertensive drugs (betablocker, ACEI, CCB), aspirin.
- Comorbidity data: family history of disorders (e.g. vascular disorders)
- Exposure data: number of completed cycles, drug concentrations
- Disease classification data - e.g. tumour grade, site and histology of primary tumour, prior therapy, time since diagnosis, number and sites of metastases, mutation and expression status of disease specific oncogenes, line of therapy.

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

- Laboratory data – including leucocyte and leucocyte subtype counts (e.g. total white blood cells (WBC), lymphocyte, monocyte or eosinophils, neutrophil to lymphocyte ration (NLR), lymphocyte to monocyte ratio (LMR), platelets to lymphocyte ration (PLR)), glucose, hemoglobin A1c (HBA1C), circulating tumour cells, calcium, total protein, total triglycerides, cholesterol, blood urea nitrogen, international normalized ratio, and anaemia.
- Other common predictors – e.g. respiratory comorbidity (e.g. asthma / chronic obstructive pulmonary disease (COPD)), other comorbid diseases (e.g. peripheral vascular disease, cerebrovascular disease, diabetes, Hepatitis C infection), simplified comorbidity score, organ dysfunction (e.g. liver, lung or renal impairment), and other clinical, biological, vital statistics, laboratory, imaging, pharmacokinetic and patient-reported outcomes measures.

Most recent data cuts of these variables are required.

Statistical Analysis Plan:

The analysis for this project will be conducted on Vivli platform.

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. Longitudinal analysis (e.g., linear, and non-linear mixed effect modelling) will be used to assess the nature and patterns of longitudinal changes of key continuous variables (e.g., drug concentration, neutrophil counts).

Crude associations will be reported based on univariate analysis (adjusting only for the study population and treatment arm), and adjusted associations based on multivariable analysis. Continuous variables will be assessed for non-linearity of association with outcomes using restricted cubic splines. Should multiple values of an assessed covariate be recorded for a single visit, the mean of the multiple reads will be used. The varying performance of clinical prediction models developed using multivariable analysis techniques including stepwise regressions, penalised methods [which minimise the risk of overfitting (e.g., elastic net analysis)], and machine learning [which excel in optimising prediction with high-dimensional data (e.g., random forest and gradient boosted methods)] will be assessed. Early markers of exposure, response and toxicity will be 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 our analyses are primarily hypothesis generating and they will require subsequent validation, 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 assessed variables, complete case analyses are 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 include evaluating the heterogeneity in outcome predictors for BTKI drugs as compared to relevant comparator. Such evaluations will allow a better understanding of whether the relationships identified are specific to a specific medicine or are common to standard treatment (i.e., common prognostic factors). Where comparisons between treatments are made we will maintain the validity of randomized design as is typical to traditional subgroup analyses of RCT data.

Predictors that have a clinically meaningful (e.g., double the risk) effect on mortality and adverse effects will be of primary interest. Based upon a 30% incidence of toxicity, a sample size of approximately 600 is required to detect a predictor (with a 10% frequency within the population) associated with a two-fold risk ($\alpha=0.05$ with 80% power). Based upon an event rate of 40% during trial follow-up (e.g., for progression), approximately 450 participants are required for 80% power to detect a predictor (with a 10% frequency within the population) associated with a two-fold hazard of the event ($\alpha=0.05$). These sample sizes are well within scope of this study.

Data will be explored for inconsistencies in time recordings, physiologically unreasonable covariate values, and unit errors. Prior to beginning analyses, individual data values will be constructed based on the raw and analysis datasets and will be checked against published manuscripts or CSRs.

Software Used:

R

Project Timeline:

The project is expected to take 1 year from the date of data access. Estimated start date 1 March 2023 with all analysis completed by 1 March 2024. Manuscripts will be drafted and submitted at each stage of the proposed project. Results will be reported back to YODA following manuscript revisions and acceptance.

Dissemination Plan:

Through this project we will publish works identifying baseline and on-treatment predictors and develop clinical prediction models of the key therapeutic and adverse outcomes of ibrutinib used in the treatment of B-cell lymphomas. Predictors will be explored based on biological and clinical plausibility and prior research – notably

including, patient characteristics, laboratory, disease classification, patient-reported outcome, concomitant medications, comorbidity, and exposure data. These domains will be explored as to whether they identify therapeutic and adverse outcomes for all patients with B-cell lymphomas or are specific to individual treatments. Samples sizes are well within scope to investigate and publish information across these degrees of freedom. It is anticipated but will be informed by analyses, that several publications may arise from this project, including for the pooled population or for predictors identified as specific to individual treatments. Manuscripts will be targeted primarily to international oncology journals (e.g. European Journal of Cancer, International Journal of Cancer, Cancers) and will be submitted as soon as possible following completion of the requisite analyses.

Bibliography:

1. Zi F, Yu L, Shi Q, Tang A, Cheng J. Ibrutinib in CLL/SLL: From bench to bedside. *Oncology reports*. 2019;42(6):2213-27.
2. Molica S, Matutes E, Tam C, Polliack A. Ibrutinib in the treatment of chronic lymphocytic leukemia: 5 years on. *Hematological Oncology*. 2020;38(2):129-36.