

## Principal Investigator

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## General Information

### Key Personnel (in addition to PI):

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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?:** Internet Search

## Conflict of Interest

[https://yoda.yale.edu/system/files/cda\\_mkm.pdf](https://yoda.yale.edu/system/files/cda_mkm.pdf)  
[https://yoda.yale.edu/system/files/cda\\_ym\\_0.pdf](https://yoda.yale.edu/system/files/cda_ym_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

### Associated Trial(s):

1. [NCT01722487 - 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 - Multicenter Phase 2 Study of Bruton's Tyrosine Kinase \(Btk\) Inhibitor, PCI-32765, in Relapsed or Refractory Mantle Cell Lymphoma](#)
3. [NCT01105247 - A Phase 1b/2 Fixed-dose Study of Bruton's Tyrosine Kinase \(Btk\) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia](#)

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all

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supporting documentation

## Research Proposal

### Project Title

Identifying clinical and electrocardiogram (ECG) findings predicting for tachyarrhythmia in patients on ibrutinib treatment

### Narrative Summary:

Ibrutinib is a novel agent oral agent used for the treatment of B cell leukemia and lymphoma patients. Its use is associated with an increased risk for atrial fibrillation (around 10%) and ventricular tachycardia was also described. We would like to study if a combination of pre- and post-treatment clinical and ECG findings can be used to identify patients at risk to develop these complications.

### Scientific Abstract:

**Background:** Atrial Fibrillation (AF) is described in up to 11% of patients treated with ibrutinib in randomized clinical trials. Development of AF may be associated with therapeutics challenges. Therefore, knowledge of the risk factors for developing AF is of clinical importance.

**Objective:** To identify and validate ECG findings associated with development of AF

**Study Design:** This is a non-interventional study that will include retrospective data review. This will be a 2 step study. Step 1 is a matched control study in order to identify ECG parameters that predict AF development. In the second step, we intend to use an historical cohort study that will include the ECG parameters found to be associated with AF at the first step, as well as patients' background clinical, demographic and echocardiographic parameters.

**Participants:** All patients older than 18 years old who were treated with ibrutinib in clinical trials will be included.

**Main Outcome Measure:** Prediction of Atrial Fibrillation

**Statistical Analysis:** The matched case control part will be analyzed by paired statistical tests, and the cohort study will be analyzed by unpaired tests. The cohort data set will be divided into learning and testing groups. A prediction model will be built based on the learning group and evaluated with the testing group.

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

Atrial Fibrillation (AF) is described in up to 11% of patients treated with ibrutinib in randomized clinical trials. Development of AF may be associated with therapeutics challenges, and administration of anticoagulants is further complicated by the increased bleeding risk associated with ibrutinib. Therefore, knowledge of the risk factors for developing AF is of clinical importance.

Similar to the general population, older age, valvular cardiac disease, male gender and comorbidities i.e. hypertension and hyperlipidemia were associated with an increased risk to develop AF in patients treated with ibrutinib. These morbidities, however, are common in the target population for ibrutinib therapy, and cannot serve as accurate predictors for the risk of AF in the individual patient.

Cardiac associated potential predictors to develop AF were previously described. Cabera and colleagues found that in patients undergoing Holter monitoring for any cause, PR interval (i.e. the distance between the ECG P and R waves), history of heart failure and age correlated with the development of new onset atrial fibrillation (NOAF). Baturova et al demonstrated that the left atrium (LA) volume predicted NOAF after stroke, while P wave terminal force correlated with AF history in patients with stroke. Another study demonstrated that prolonged PR interval > 200 ms and PR variations in different ECGs were predictors of NOAF in patients with frequent premature atrial beats. Finally, Magne et al showed that history of AF and LA size are the best predictors of AF post coronary bypass surgery.

In accordance with the above studies our aim is to study whether cardiac specific parameters, in addition to baseline demographics and comorbidities, can predict the occurrence of AF in patients who receive Ibrutinib.

### Specific Aims of the Project:

Specific aim 1: To identify ECG parameters that predict AF development

Specific aim 2: To develop a prediction model using ECG and clinical findings for the development of AF in patients treated with ibrutinib

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

New research question to examine treatment safety  
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:**

We will retrieve data from clinical trials of patients receiving ibrutinib for chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma

Main inclusion criteria:

1. Treatment with Ibrutinib in a randomized clinical trial
2. Available clinical data
3. Available baseline ECG

Main exclusion criteria:

Did not receive Ibrutinib

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

The main outcome is the development of atrial fibrillation

This event should be defined as an adverse event (AE) or a serious adverse event (SAE) in specific patient's data file

We will, therefore screen all AE and SAE of the study population for these events

Once identified, we will review all CRF details regarding the specific event in order to verify it is indeed an atrial fibrillation, and validate the patient was on ibrutinib

Only verified cases will be included in the trial

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

We will collect the following variables:

1. Baseline ECG parameters: P wave height and width in lead 2, P wave terminal force in V1 (duration of the negative part x depth), QRS width, QT interval and PR interval. Also, the change in PR, QRS (i.e. the length between the start of ECG Q wave and end of the S wave) and QT (i.e. the length between the end of ECG Q wave and end of the T wave) intervals when compared at baseline and 1 month after initiation of Ibrutinib.
2. Echocardiographic parameters: Ejection fraction, LA volume, diastolic dysfunction and valvular disease.
3. Clinical parameters: CHADS2 VASC score (CHF history, Hypertension, Age, Diabetes, Stroke history, Vascular disease, Sex Category), HAS-BLED score (Hypertension, Abnormal renal function, Stroke history, Bleeding predisposition, Labile INR, Elderly, Drugs predisposing to bleeding or alcohol) and body mass index (BMI).
4. Laboratory parameters: creatinine, blood count

Clinical and laboratory data will be collected from the CRF

ECG data will be collected by reviewing each individual ECG by one of the investigators

**Statistical Analysis Plan:**

This is a 2 step study.

In step 1, we intend to conduct a matched control study in order to identify ECG parameters that may predict AF development. For the matched case control study, we will use 1:1 matching ratio (age and gender matched). Since we plan to compare several parameters between the group, we defined a conservative significance level of 1%. The power was set to 80%. In order to identify a difference of 0.5 standard deviation we will need 51 pairs (paired T test) for continuous variables. For categorical variables, in order to identify a 25% difference, between the matched sets we will need 91 pairs (McNemar test).

In the second step, we intend to use an historical cohort study that will include the ECG parameters that were found to be associated with AF at the first step, as well as patients' background clinical demographic and echocardiographic parameters as detailed above. For this part of the study, in order to identify a difference of 0.5 standard deviation we will need 188 patients for continuous variables (Intendent samples T test). While 298 patients will be needed in order to find 20% difference in categorical variables (Chi square test).

Categorical variables will be reported as frequencies and percentages and continuous variables will be reported as means and standard deviations (SD) or medians and interquartile ranges (IQR). Continuous variables will be evaluated for normal distribution using histograms and Q-Q Plots. For the matched case control study, we will use McNemar test to compare categorical variables and paired samples T-test or Wilcoxon test for the continuous variables.

Conditional logistic regression will be used for multi variate analysis. Parameters that will be found to be associated with AF development at a significance level of  $p < 0.2$  will be included in the regression model.

For the cohort study the data set will be randomly divide into learning group (80%) and testing group (20%). In order to identify AF predictors, categorical variables will be compared using Chi-square test or Fisher's exact test and continuous variables by independent samples t-test or by Mann Whitney test. Multivariate logistic regression will be used to build a prediction equation. The logistic regression will include all studied variables which will be removed from the model by a selection criteria using backward stepwise likelihood ratio method.

Hosmer–Lemeshow goodness of fit test will be used to evaluate the regressing model.

The discrimination ability of the model will be described using the area under the Receiver operating characteristic curve and the discrimination slope using box and whisker plot.

The model will be validated using the testing group. Specificity, sensitivity. Positive and negative predictive value and accuracy will be reported.

A two-tailed  $p < 0.05$  will be considered statistically significant.

### **Project Timeline:**

Anticipated project start date : June 1st, 2019

Analysis completion date: May 31st, 2020

Manuscript drafted and first submitted for publication: August 31st, 2020

Results reported back to the YODA Project: September 30th, 2020

### **Dissemination Plan:**

Target audience are physicians and nurses practicing hematology, hemto-oncology and cardiology

Potentially suitable journal for subimission are Q1/Q2 Hematology journals

### **Bibliography:**

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