**Research Proposal**

**Project Title**

Identifying Prognostic and Predictive Factors for Causal Exposure-Response Analysis of Ibrutinib in treatment of non-Hodgkin Lymphoma

**Scientific Abstract**

Dose optimization has become a pivotal component of oncology drug development. In clinical trials, Exposure-Response (E-R) analyses serve as an essential step to support dose selection. Nevertheless, it’s challenging to derive a causal E-R relationship due to the presence of heterogeneous treatment effects (HTE)1. To achieve a better understanding of causal E-R relationships, it’s important to identify the confounding factors, including prognostic and predictive factors, that affect patient health outcomes and to quantify their effects on E-R relationships. In this study, we aim to evaluate the E-R relationship of ibrutinib in treatment of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) or Waldenström's macroglobulinemia (WM) and identify critical prognostic and predictive factors influencing patient response and survival. Our approach will entail the application of data-mining techniques and causal inference methods to uncover prognostic and predictive factors and further elucidate the causal E-R relationship of ibrutinib based on subgroup analysis.

**Brief Project Background and Statement of Project Significance**

CLL, SLL, and WM are three slow-growing types of non-Hodgkin lymphoma (NHL). Ibrutinib, a covalent inhibitor of Bruton’s tyrosine kinase (BTK), has become one of the promising target therapies in treating these diseases2. Considering their slight differences in clinical features, the E-R relationships of ibrutinib may be shaped in different ways by different disease features. However, conventional E-R analyses were usually conducted based on a pooled population2. Understanding how disease features as well as other patient demographic factors such as genetic mutations influence patient response and survival is important for deriving a causal E-R relationship and for dose optimization. Heterogeneous treatment effects (HTE) analyses can help identify critical confounding factors and elucidate causal E-R relationships. Using ibrutinib as an example, this study aims at elucidating how the E-R relationships are shaped by different prognosis or risk levels and how the derived causal E-R relationships better support of dose optimization based on individual outcomes.

**Specific Aims of the Project**

This study aims to analyze clinical trial data to identify critical prognostic and predictive factors and derive causal E-R relationships of ibrutinib in treatment of three NHLs: CLL, SLL, and WM. This study is proposed with two specific aims:

Aim 1: To identify critical prognostic and predictive factors to patient response and clinical outcome and to quantify their influences on NHL patient response and survival.

Aim 2: To derive a causal E-R relationship for ibrutinib in treatment of NHL and demonstrate it as an example for dose optimization at early stage of drug development.

**Study Design**

This study will assemble the clinical data of NHL patients receiving ibrutinib with combined agents. HTE analyses will be performed to identify potential prognostic and predictive factors that influence NHL patient response and survival. Several strategies, including conventional subgroup HTE approach, risk-based HTE approach, and effect-based HTE approach3, will be employed to subgroup patients and evaluate treatment effects. The E-R relationship of ibrutinib will be analyzed within subgroups.

The datasets we request are preferably to include detailed information on patient demographic characteristics, disease/treatment history, toxicity profiles, and clinical outcomes. The pharmacokinetics data of ibrutinib, if any, are also desirable.

**Purpose of Analysis**

This study seeks to identify critical prognostic and predictive factors affecting NHL patient response and survival outcomes and to derive causal E-R relationships of ibrutinib in treatment of CLL, SLL or WM.

**Research Methods**

To achieve our research goals, several analyses will be conducted:

1. Data cleaning: Develop inclusion/exclusion criteria to select patients eligible for analyses. Evaluate the presence of missing data and establish an appropriate methodology for addressing and managing such data gaps.
2. Conventional subgroup analyses: For each potential critical factor, stratify patients into subgroups based on the specific factor and estimate the treatment effect within each subgroup.
3. Risk-based HTE approach: Construct a comprehensive risk model that incorporates multiple covariates, including demographics and disease-related variables, to compute personalized risk scores for each patient. Stratify patients into subgroups based on varying levels of predicted risk scores. Estimate the treatment effect of each subgroup.
4. Effect-based HTE approach: Develop a model to predict treatment effect based on multiple characteristics. Predict the treatment effect for each patient. Stratify patients into subgroups based on their predicted treatment effects. Estimate the real treatment effect for each subgroup.
5. Characterize ibrutinib exposure in individual patients: Develop a popPK model including covariate effects to describe the ibrutinib exposure at disease compartment for each individual patient.
6. Derive casual E-R relationships: Evaluate the relationship between predicted ibrutinib exposure and patient response within each subgroup.

**Software to be used**

R and Monolix

**Data Source and Inclusion/Exclusion Criteria**

Adult patients receiving ibrutinib and/or other relevant agents for the treatment of CLL, SLL, or WM from studies NCT02264574, NCT01578707, and NCT02165397. The following variables are requested:

1. Demographic variables: age, sex, race, height, body weight, ECOG performance-status score, number of lines of previous therapy, hepatic impairment, renal impairment, etc.
2. Disease-related variables: time since diagnosis, del17p, TP53 mutation, del 11q, Immunoglobulin Heavy Chain Variable Region (IGHV) mutation, hemoglobin level at baseline, etc.
3. Treatment-related variables: dosage, dosing schedule, duration of treatment, concomitant medications, etc.
4. Outcome measure: Progression Free Survival (PFS), Overall Response Rate (ORR), Overall Survival (OS), Rate of Minimal Residual Disease (MRD), Rate of Sustained Hemoglobin Improvement, etc.
5. PK data: ibrutinib concentration-time profile.

**Primary Outcome Measure**

Progression Free Survival (PFS)

**Secondary Outcome Measure**

Overall Response Rate (ORR), Overall Survival (OS), Rate of Minimal Residual Disease (MRD), Rate of Sustained Hemoglobin Improvement, Toxicity and Tolerability

**Main Predictor/Independent Variable**

Demographic variables: age, sex, race, height, body weight, ECOG performance-status score, number of lines of previous therapy, hepatic impairment, renal impairment, etc.

Disease-related variables: time since diagnosis, del17p, TP53 mutation, del 11q, Immunoglobulin Heavy Chain Variable Region (IGHV) mutation, hemoglobin level at baseline, etc.

Treatment-related variables: dosage, dosing schedule, duration of treatment, concomitant medications, etc.

Therapeutic exposure: ibrutinib dosage, dose modifications, pharmacokinetic measurements

**Statistical Analysis Plan**

The statistical analysis plan for this research project is designed to rigorously evaluate the exposure-response relationship of ibrutinib in treatment of CLL, SLL or WM. It encompasses a comprehensive approach involving various statistical techniques and models to achieve the specific aims of the study. The analysis plan is divided into several key components:

Descriptive Statistics: Descriptive statistics will be employed to provide an overview of the dataset. This includes suarizing patient demographics, disease characteristics, and the distribution of ibrutinib concentrations. We will also examine the distribution of patient PFS and secondary endpoints such as OS, ORR, and rate of MRD to gain a preliminary understanding of the data.

Population Pharmacokinetics (popPK) Model: To understand the pharmacokinetic behavior of ibrutinib in individual patients, a population pharmacokinetics (popPK) model which accounts for multiple covariates will be employed to characterize the concentration-time profiles of ibrutinib following administration of specific dosage.

Risk Model Development: A logistic regression risk prediction model for response will be developed involving multiple potential risk predictors to compute a risk score for each individual.

Effect Model Development: A causal forest model will be developed using randomly selected half dataset to predict the treatment effect based on multiple characteristics.

Subgroup Stratification: Patients will be stratified into subgroups based on varying levels of risk scores or predicted treatment effects.

Dose-Response Analysis: The primary focus of this research is to investigate the dose-response relationship of ibrutinib within defined subgroups. Logistic regression analyses will be employed to evaluate the relationship between ibrutinib exposure (predicted by the popPK model) and patient response.

**Project Timeline:**

The project is expected to take 1 year from the date of data access. Estimated start date 1 January 2024 with all analysis completed by 1 January 2025. Manuscripts will be drafted and submitted after completion of the proposed project. Results will be reported back to YODA following manuscript revisions and acceptance.

**References**

1. Gong X, Hu M, Basu M, Zhao L. Heterogeneous treatment effect analysis based on machine-learning methodology. *CPT: Pharmacometrics & Systems Pharmacology*. 2021;10(11):1433-1443.

2. Munir T, Brown JR, O’Brien S, et al. Final analysis from RESONATE: Up to six years of follow‐up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353-1363.

3. Goligher EC, Lawler PR, Jensen TP, et al. Heterogeneous Treatment Effects of Therapeutic-Dose Heparin in Patients Hospitalized for COVID-19. *JAMA*. 2023;329(13):1066.