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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: Food and Drug Administration

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

<https://yoda.yale.edu/wp-content/uploads/2023/10/COI-Cao.pdf>

https://yoda.yale.edu/wp-content/uploads/2023/10/COI-Form_XL.pdf

https://yoda.yale.edu/wp-content/uploads/2023/10/Viet-Dang_-_COI-1.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. [NCT01578707 - 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](#)
2. [NCT02165397 - 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](#)
3. [NCT02264574 - 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

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

Narrative Summary:

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.

Scientific Abstract:

Background: 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.

Objective: This study seeks to identify critical prognostic and predictive factors affecting non-Hodgkin Lymphoma (NHL) patient response and survival outcomes and derive causal E-R relationships of ibrutinib in treatment of NHL.

Study Design: This study will assemble the clinical data of NHL patients receiving ibrutinib and relevant 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 approach², will be employed to subgroup patients and evaluate treatment effects. The E-R relationship of ibrutinib will be analyzed within subgroups.

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

Primary and Secondary Outcome Measure(s): The primary outcome measure is patient response based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria (for

CLL and SLL patients) or the modified V1th International Workshop on Waldenström's Macroglobulinemia (IWWM) criteria (for WM patients). The secondary outcome measures include time to progression (TTP), duration of response, progression-free survival (PFS), and overall survival (OS).

Statistical Analysis: Descriptive statistics will be employed to provide an overview of the dataset. A population pharmacokinetics (popPK) model which accounts for multiple covariates will be employed to characterize the concentration-time profiles of ibrutinib for each individual. HTE analyses will be employed to subgroup patients based on risk prediction model or effect model. E-R analyses will be performed for each subgroup.

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:

Methodological research

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

Preliminary research to be used as part of a grant proposal

Develop or refine statistical methods

Research on clinical trial methods

Research Methods

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

Adult patients receiving ibrutinib and/or other relevant agents for the treatment of CLL, SLL, or WM from studies NCT02264574, NCT01578707, and NCT02165397. Inclusion criteria: (1) Patients must be 18 Years and older (Adult, Older Adult); (2) Patients have been diagnosed with CLL, SLL or WM; (3) Patients have received ibrutinib or comparator drugs for treatment of CLL, SLL, or WM. 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 and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary outcome measure is the Progression Free Survival (PFS), defined as time from the date randomization to the date of first IRC-confirmed disease progression (PD) or date of death due to any cause, whichever occurred first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death⁴. The assessment of PD was based on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria (for CLL and SLL patients) or the modified Vth International Workshop on Waldenström's Macroglobulinemia (IWWM) criteria (for WM patients).

The IWCLL 2008 criteria categorizes patient response into four types: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). The details of response definition can be found in Hallek et al.⁵

The modified Vth International Workshop on Waldenström's Macroglobulinemia (IWWM) criteria categorizes patient response into six types: complete response (CR), very good partial response (VGPR), partial response (PR), minor response (MR), stable disease (SD), and progressive disease (PD). The details of response definition can be found in Owen et al.⁶

The secondary outcome measures include:

1. Overall Response Rate (ORR): Percentage of participants achieving a best overall response of complete response (CR) or partial response (PR) per IRC assessment.
2. Overall Survival (OS): The time from the date of randomization to the date of death from any cause. All deaths observed as the time of the analysis were considered as events.
3. Rate of Minimal Residual Disease (MRD): Percentage of participants who achieved MRD-negative response, defined as < 1 CLL cell per 10,000 leukocytes as assessed by flow cytometry of a bone marrow aspirate per central laboratory⁴.
4. Rate of Sustained Hemoglobin Improvement: Percentage of participants with sustained hemoglobin improvement, defined as hemoglobin increase 2 g/dL over baseline continuously for 56 days without blood transfusions or growth factors⁴.
5. Toxicity and Tolerability: Any treatment-related adverse events.

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

The main predictor is the exposure of ibrutinib, which includes:

1. Ibrutinib dosage: The quantity of ibrutinib prescribed to each patient.
2. Timing of Administration: The precise schedule and timing at which ibrutinib is administered to patients.
3. Ibrutinib Concentration-Time Profiles: This factor involves monitoring and analyzing the concentration of ibrutinib within the patient's bloodstream over time.

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

Demographic variables:

- Age: The age of the patient at the moment of their enrollment into a study or medical program, typically measured in years.

- Sex: The biological classification of the patient as either female or male, representing their gender identity.
- Race: The patient's ethnic or racial background, which may encompass various categories or self-identifications, depending on the study's criteria.
- Height: The vertical measurement of a patient's stature, typically recorded in units such as centimeters or inches.
- Body weight: The mass or weight of the patient's body, often measured in kilograms or pounds, providing information about their physical size.
- ECOG performance-status score: The Eastern Cooperative Oncology Group (ECOG) performance-status score is a measure used in oncology to assess a patient's overall physical condition and ability to perform daily activities. It is typically graded on a scale from 0 (fully active) to 5 (deceased).
- Number of lines of previous therapy: The count of distinct treatment regimens or lines of therapy that the patient has undergone before the current study or medical intervention.
- Hepatic impairment: The extent to which the patient's liver function may be compromised or impaired, which can be assessed through various clinical indicators and tests.
- Renal impairment: The degree of dysfunction or impairment in the patient's kidneys, often assessed by measures such as creatinine clearance or glomerular filtration rate (GFR), indicating the kidneys' ability to filter waste from the blood.

Disease-related variables:

- Time Since Diagnosis: The period that has elapsed from the time a patient was initially diagnosed with CLL, SLL or WM, typically measured in years or months.
- Cumulative Illness Rating Score (CIRS)
- Creatinine clearance estimated using Cockcroft-Gault equation.
- Del17p: The loss of the short arm of chromosome 17 determined by fluorescence in situ hybridization (FISH).
- TP53 mutation: Mutations in TP53 gene determined by polymerase chain reaction (PCR) or Next Generation Sequencing.
- Del 11q: Deletions in the long arm of chromosome 11 determined by FISH.
- Immunoglobulin Heavy Chain Variable Region (IGHV) mutation.
- Hemoglobin level at baseline

Treatment-related variables:

- Concomitant medications: Concomitant medications refer to any additional drugs or therapies that a patient is prescribed or receiving alongside ibrutinib.
- Prior exposure to BTK inhibitors.

Statistical Analysis Plan:

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.

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 summarizing 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.

Software Used:

R

Project Timeline:

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.

Dissemination Plan:

Manuscripts will be drafted and submitted to Clinical Pharmacology & Therapeutics, Cancer Research, or Journal for ImmunoTherapy of Cancer after completion of the proposed project. The analyses aim to identify the key prognostic and predictive factors for treating CLL, SLL, or WM. Our method will underscore the importance of adjusting these significant covariates in randomized clinical trials to enhance our decision-making regarding drug effectiveness and optimal dosages.

Bibliography:

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.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2023/10/Research_Proposal_Ibrutinib_carter-cao-at-

[UNC.docx](#)