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SCOPUS ID:
Requires Data Access? Yes

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/wp-content/uploads/2022/12/COI-Form-CK.pdf
https://yoda.yale.edu/wp-content/uploads/2022/12/COI-FORM-MA.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. NCT02195869 - PCYC-1129-CA - A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease

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

Research Proposal

Project Title

CYP3A4 Interactions and Adverse Drug Reactions in Ibrutinib Therapy: Revisting multiple clinical trials

Narrative Summary:

The proposed study aims to investigate the prevalence and clinical consequences of drug-drug interactions involving the CYP3A4 enzyme in patients treated with ibrutinib. Ibrutinib is an oral chemotherapy medication that is used to treat chronic lymphocytic leukemia and mantle cell lymphoma. It is metabolized by the CYP3A4 enzyme, and interactions with other medications that affect the activity of this enzyme can alter ibrutinib plasma concentrations and potentially affect its efficacy and safety.
Understanding the impact of CYP3A4 interactions on ibrutinib plasma concentrations and ADRs is important for optimizing ibrutinib treatment and minimizing ADRs.

Scientific Abstract:

Background: Ibrutinib is an oral, first-in-class, Bruton's tyrosine kinase inhibitor approved for the treatment of chronic lymphocytic leukemia and mantle cell lymphoma. It is metabolized by the CYP3A4 enzyme, and drug-drug interactions with CYP3A4 inhibitors or inducers can alter ibrutinib plasma concentrations and potentially affect its efficacy and safety.
Objective: The purpose of this study is to investigate the prevalence and clinical consequences of CYP3A4 interactions in patients treated with ibrutinib.
Study Design: This is a retrospective, observational study using patient level data from previous controlled clinical ibrutinib trials.
Participants: The study population includes adult patients who were included in the clinical studies of ibrutinib.
Primary Outcome Measure: The primary outcome is the incidence of adverse drug reactions (ADRs) in patients with and without CYP3A4 interactions.
Secondary Outcome Measures: The secondary outcomes include the effect of CYP3A4 interactions on ibrutinib plasma concentrations and the relationship between ibrutinib plasma concentrations and ADRs.
Statistical Analysis: Descriptive statistics will be used to characterize the study population and the prevalence of CYP3A4 interactions. The incidence of ADRs will be compared between patients with and without CYP3A4 interactions using chi-square or Fisher's exact test. The relationship between ibrutinib plasma concentrations and ADRs will be analyzed using Pearson's correlation coefficient. All statistical tests will be two-tailed and a p-value

Brief Project Background and Statement of Project Significance:

Ibrutinib is a widely-used oral chemotherapy medication that is metabolized by the CYP3A4 enzyme. Drug-drug interactions with CYP3A4 inhibitors or inducers can alter ibrutinib plasma concentrations and potentially affect its efficacy and safety. The proposed study aims to investigate the prevalence and clinical consequences of CYP3A4 interactions in patients treated with ibrutinib.
Understanding the impact of CYP3A4 interactions on ibrutinib plasma concentrations and adverse

drug reactions (ADRs) is important for optimizing ibrutinib treatment and minimizing ADRs. The results of this study will provide valuable information for healthcare providers and researchers, allowing them to better understand the potential consequences of CYP3A4 interactions and make informed decisions about ibrutinib treatment.
This research is significant because it will contribute to the existing body of knowledge on ibrutinib and its interactions with other medications, and it will inform the development of guidelines and recommendations for the safe and effective use of ibrutinib. This information will be beneficial for patients, healthcare providers, and researchers, and it has the potential to materially enhance generalizable scientific and medical knowledge to inform science and public health.

Specific Aims of the Project:

The specific aims of the project are as follows:
To determine the prevalence of CYP3A4 interactions in patients treated with ibrutinib.
To evaluate the effect of CYP3A4 interactions on ibrutinib plasma concentrations.
To assess the incidence of ADRs in patients with and without CYP3A4 interactions.
To examine the relationship between ibrutinib plasma concentrations and ADRs.
The study objectives are:
To characterize the prevalence of CYP3A4 interactions in patients treated with ibrutinib.
To assess the impact of CYP3A4 interactions on ibrutinib plasma concentrations.
To compare the incidence of ADRs between patients with and without CYP3A4 interactions.
To examine the relationship between ibrutinib plasma concentrations and ADRs.
The specific hypotheses to be evaluated are:
CYP3A4 interactions are prevalent in patients treated with ibrutinib.
CYP3A4 interactions alter ibrutinib plasma concentrations.
Patients with CYP3A4 interactions have a higher incidence of ADRs compared to those without CYP3A4 interactions.
There is a relationship between ibrutinib plasma concentrations and ADRs.

Study Design:

Meta-analysis (analysis of multiple trials together)

Research Methods

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

Inclusion criteria:
Adult patients (age ? 18 years)
Prescribed ibrutinib for the treatment of chronic lymphocytic leukemia or mantle cell lymphoma

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

Primary Outcome Measure: The primary outcome is the incidence of adverse drug reactions (ADRs) in patients with and without CYP3A4 interactions.
Secondary Outcome Measures: Overall survival, progression-free survival and the effect of CYP3A4 interactions on ibrutinib plasma concentrations and the relationship between ibrutinib plasma concentrations and ADRs.
ADRs will be identified from the adverse event reports in the clinical trial by systematically reviewing and analyzing all reported adverse events. We will start with the known important ADRs such as artrial fibriliation and neutropenia. We will then compare the incidence of these adverse reactions in persons with CYP3A4 inhibitors with persons without to determine if there is a significant difference between the two groups. Any adverse reactions that occur at a higher rate in the treatment group than in the control group will be considered to be related to the study drug.

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

The reviewer has raised a valid concern about the availability of information on CYP3A4 inhibitors for the proposed trials. It is important to note that the exclusion criteria for one of the trials, specifically the requirement for treatment with a strong CYP3A4/5 and/or CYP2D6 inhibitor, may limit the ability to conduct the proposed analyses on the effects of CYP3A4 interactions on ibrutinib plasma concentrations.
The primary focus of this study is the impact of CYP3A4 interactions on ibrutinib plasma concentrations. To investigate this, the study will be looking at the presence or absence of CYP3A4 interactions during ibrutinib treatment. CYP3A4 interactions will be defined as the concurrent use of ibrutinib with a CYP3A4 inhibitor or inducer. The list of CYP3A4 inhibitors and inducers will be based on the most current recommendations from the US Food and Drug Administration and other reputable sources. Additionally, because of the exclusion criteria mentioned, the team will categorize the CYP3A4 inhibitors into mild, moderate, and severe categories in order to estimate the effect of each category separately.

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

Demographic variables: age, gender, race/ethnicity
Clinical variables: diagnosis (chronic lymphocytic leukemia or mantle cell lymphoma), stage of disease, prior treatment, comorbidities
Ibrutinib treatment variables: dose, duration of treatment, concomitant medications
CYP3A4 interaction variables: type (inhibitor or inducer), duration of use, dose
Adverse drug reaction variables: type, severity, outcome (resolved or ongoing)
These variables will be collected from electronic medical records and will be defined as follows:
Demographic variables:
Age: patient's age at the time of ibrutinib treatment
Gender: male or female
Race/ethnicity: self-reported race/ethnicity of the patient
Clinical variables:
Diagnosis: chronic lymphocytic leukemia or mantle cell lymphoma
Stage of disease: based on the most current staging system for the respective diagnosis
Prior treatment: type and duration of any previous treatment for the diagnosis
Comorbidities: other medical conditions present at the time of ibrutinib treatment
Ibrutinib treatment variables:
Dose: daily dose of ibrutinib
Duration of treatment: total length of ti

Statistical Analysis Plan:

The statistical analysis plan for this study will include both descriptive and inferential statistics. Descriptive statistics will be used to characterize the study population, including the prevalence of CYP3A4 interactions, the distribution of demographic and clinical variables, and the incidence of ADRs. Measures of central tendency (e.g. mean, median) and dispersion (e.g. standard deviation, range) will be calculated for continuous variables, and frequencies and percentages will be calculated for categorical variables.
Bivariate analyses will be conducted to examine the association between the main independent variable (CYP3A4 interactions) and the primary and secondary outcome measures. Chi-square or Fisher's exact test will be used to compare the incidence of ADRs between patients with and without CYP3A4 interactions. Pearson's correlation coefficient will be used to assess the relationship between ibrutinib plasma concentrations and ADRs.
Multivariable analyses will be conducted to adjust for potential confounders and to assess the independent effect of CYP3A4 interactions on the outcome measures. Logistic regression will be used to examine the association between CYP3A4 interactions and the incidence of ADRs, adjusting for demographic and clinical variables. Linear regression will be used to examine the association between CYP3A4 interactions and ibrutinib plasma concentrations, adjusting for demographic and

clinical variables.
In addition to the above analyses, further advanced analyses may be conducted depending on the specific research question and study design. For example, propensity score methods may be used to control for confounding in the analysis of the relationship between CYP3A4 interactions and ADRs. Kaplan-Meier or Cox modeling approaches may be used to evaluate the effect of CYP3A4 interactions on time-to-event outcomes, such as disease progression or survival. Non-parametric testing may be used for variables that do not follow a normal distribution.
All statistical tests will be two-tailed and a p-value

Project Timeline:

The timeline for the proposed study is as follows:
Anticipated project start date: 2 months after approval of the data request
Data cleaning and preparation: 1 month
Statistical analysis: 2 months
Manuscript drafting: 3 months
Manuscript review and revision: 2 months
Manuscript submission: 1 month
Results reported back to the YODA Project: 2 months after manuscript acceptance

Dissemination Plan:

The primary product of the completed research project will be a manuscript reporting the findings of the study. The manuscript will be written in accordance with the standards of a peer-reviewed scientific journal and will include a clear and concise description of the study objectives, methods, results, and conclusions.
The target audience for the manuscript will be healthcare providers and researchers who are interested in ibrutinib treatment and drug-drug interactions involving CYP3A4. The manuscript will be suitable for submission to a general or specialty medical journal with a focus on oncology, hematology, or pharmacology. Some examples of suitable journals for submission include the Journal of Clinical Oncology, Blood, and Clinical Pharmacology and Therapeutics.
In addition to the manuscript, other products of the study may include presentations at scientific conferences, posters, and webinars. The target audience for these products will be similar to that of the manuscript and will include healthcare providers and researchers who are interested in ibrutinib treatment and drug-drug interactions involving CYP3A4.
The results of the study will also be reported back to the YODA Project as per the Data Use Agreement.

Bibliography:

1: Langerbeins P, Zhang C, Robrecht S, Cramer P, Frstenau M, Al-Sawaf O, von Tresckow J, Fink AM, Kreuzer KA, Vehling-Kaiser U, Tausch E, Mller L, Eckart MJ, Schlag R, Freier W, Gaska T, Balser C, Reiser M, Stauch M, Wendtner CM, Fischer K, Stilgenbauer S, Eichhorst B, Hallek M. The CLL12 trial: ibrutinib vs placebo in treatment-nave, early-stage chronic lymphocytic leukemia. Blood. 2022 Jan 13;139(2):177-187. doi: 10.1182/blood.2021010845. PMID: 34758069.
2: Xu RA, Wen J, Tang P, Wang C, Xie S, Zhang BW, Zhou Q, Cai JP, Hu GX. Functional Characterization of 22 CYP3A4 Protein Variants to Metabolize Ibrutinib In Vitro. Basic Clin Pharmacol Toxicol. 2018 Apr;122(4):383-387. doi: 10.1111/bcpt.12934. Epub 2017 Nov 30. PMID: 29117640.
3: Rood JJM, Jamalpoor A, van Hoppe S, van Haren MJ, Wasmann RE, Janssen MJ, Schinkel AH, Masereeuw R, Beijnen JH, Sparidans RW. Extrahepatic metabolism of ibrutinib. Invest New Drugs. 2021 Feb;39(1):1-14. doi: 10.1007/s10637-020-00970-x. Epub 2020 Jul 4. PMID: 32623551; PMCID: PMC7851014.
4: Hardy-Abeloos C, Pinotti R, Gabrilove J. Ibrutinib dose modifications in the management of CLL. J Hematol Oncol. 2020 Jun 5;13(1):66. doi: 10.1186/s13045-020-00870-w. PMID: 32503582; PMCID: PMC7275592.
5: de Zwart L, Snoeys J, De Jong J, Sukbuntherng J, Mannaert E, Monshouwer M.

Ibrutinib Dosing Strategies Based on Interaction Potential of CYP3A4 Perpetrators Using Physiologically Based Pharmacokinetic Modeling. Clin Pharmacol Ther. 2016 Nov;100(5):548-557. doi: 10.1002/cpt.419. Epub 2016 Aug 27. PMID: 27367453.
6: Han M, Qian J, Ye Z, Xu R, Chen D, Xie S, Cai J, Hu G. Functional assessment of the effects of CYP3A4 variants on acalabrutinib metabolism in vitro. Chem Biol Interact. 2021 Aug 25;345:109559. doi: 10.1016/j.cbi.2021.109559. Epub 2021 Jun 18. PMID: 34153224.
7: de Jong J, Mitselos A, Jurczak W, Cordoba R, Panizo C, Wrobel T, Dlugosz-Danecka M, Jiao J, Sukbuntherng J, Ouellet D, Hellemans P. Ibrutinib does not have clinically relevant interactions with oral contraceptives or substrates of CYP3A and CYP2B6. Pharmacol Res Perspect. 2020 Oct;8(5):e00649. doi: 10.1002/prp2.649. PMID: 32945596; PMCID: PMC7506988.
8: Kronabel D. Possible influence of some foods on the metabolism of ibrutinib. Clin Lab. 2015;61(3-4):443-4. doi: 10.7754/clin.lab.2015.150116. PMID: 25975016.
9: Wen J, Bao SS, Zhang BW, Liu TH, Ou-Yang QG, Cai JP, Zhou HY. Inhibitory effect of resveratrol on the pharmacokinetic of ibrutinib by UPLC-MS/MS. Drug Dev Ind Pharm. 2019 Jan;45(1):27-31. doi: 10.1080/03639045.2018.1514044. PMID: 30156133.
10: Lee J, Fallon JK, Smith PC, Jackson KD. Formation of CYP3A-specific metabolites of ibrutinib in vitro is correlated with hepatic CYP3A activity and 4?-hydroxycholesterol/cholesterol ratio. Clin Transl Sci. 2022 Nov 9. doi: 10.1111/cts.13448. Epub ahead of print. PMID: 36350327.
11: Tapaninen T, Olkkola AM, Tornio A, Neuvonen M, Elonen E, Neuvonen PJ, Niemi M, Backman JT. Itraconazole Increases Ibrutinib Exposure 10-Fold and Reduces Interindividual Variation-A Potentially Beneficial Drug-Drug Interaction. Clin Transl Sci. 2020 Mar;13(2):345-351. doi: 10.1111/cts.12716. Epub 2019 Nov 29. PMID: 31664782; PMCID: PMC7070818.
12: de Jong J, Hellemans P, De Wilde S, Patricia D, Masterson T, Manikhas G, Myasnikov A, Osmanov D, Crdoba R, Panizo C, de Zwart L, Snoeys J, Chauhan V, Jiao J, Sukbuntherng J, Ouellet D. A drug-drug interaction study of ibrutinib with moderate/strong CYP3A inhibitors in patients with B-cell malignancies. Leuk Lymphoma. 2018 Dec;59(12):2888-2895. doi: 10.1080/10428194.2018.1460474. Epub 2018 May 30. PMID: 29846137.
13: Tedeschi A, Frustaci AM, Mauro FR, Chiarenza A, Coscia M, Ciolli S, Reda G, Laurenti L, Varettoni M, Murru R, Barat C, Sportoletti P, Greco A, Borella C, Rossi V, Deodato M, Biagi A, Zamprogna G, Pelle AC, Lapietra G, Vitale C, Morelli F, Cassin R, Fresa A, Cavalloni C, Postorino M, Ielo C, Cairoli R, Di Raimondo F, Montillo M, Del Poeta G. Do age, fitness, and concomitant medications influence management and outcomes of patients with CLL treated with ibrutinib? Blood Adv. 2021 Dec 28;5(24):5490-5500. doi: 10.1182/bloodadvances.2021004824. PMID: 34525181; PMCID: PMC8714729.
14: Ly JQ, Messick K, Qin A, Takahashi RH, Choo EF. Utility of CYP3A4 and PXR-CAR-CYP3A4/3A7 Transgenic Mouse Models To Assess the Magnitude of CYP3A4 Mediated Drug-Drug Interactions. Mol Pharm. 2017 May 1;14(5):1754-1759. doi: 10.1021/acs.molpharmaceut.7b00006. Epub 2017 Apr 7. PMID: 28345929.
15: Finnes HD, Chaffee KG, Call TG, Ding W, Kenderian SS, Bowen DA, Conte M, McCullough KB, Merten JA, Bartoo GT, Smith MD, Leis J, Chanan-Khan A, Schwager SM, Slager SL, Kay NE, Shanafelt TD, Parikh SA. Pharmacovigilance during ibrutinib therapy for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in routine clinical practice. Leuk Lymphoma. 2017 Jun;58(6):1376-1383. doi: 10.1080/10428194.2016.1251592. Epub 2016 Nov 8. PMID: 27820970; PMCID: PMC5364094.
16: van Hoppe S, Rood JJM, Buil L, Wagenaar E, Sparidans RW, Beijnen JH, Schinkel AH. P-Glycoprotein (MDR1/ABCB1) Restricts Brain Penetration of the Bruton’s Tyrosine Kinase Inhibitor Ibrutinib, While Cytochrome P450-3A (CYP3A) Limits Its Oral Bioavailability. Mol Pharm. 2018 Nov 5;15(11):5124-5134. doi: 10.1021/acs.molpharmaceut.8b00702. Epub 2018 Oct 10. PMID: 30247919.

17: Lambert Kuhn E, Levque D, Lioure B, Gourieux B, Bilbault P. Adverse event potentially due to an interaction between ibrutinib and verapamil: a case report. J Clin Pharm Ther. 2016 Feb;41(1):104-5. doi: 10.1111/jcpt.12355. PMID: 26813987.
18: Santoro RC, Falbo M, Levato L, Iannaccaro P, Prejan S. Dabigatran in ibrutinib-treated patients with atrial fibrillation and chronic lymphocytic leukemia: experience of three cases. Blood Coagul Fibrinolysis. 2021 Mar 1;32(2):159-161. doi: 10.1097/MBC.0000000000000981. PMID: 33273263.
19: Wasserstrum Y, Raanani P, Kornowski R, Iakobishvili Z. Concomitant Treatment with Ibrutinib and Amiodarone Causing Reversible Heart Failure Syndrome. Isr Med Assoc J. 2016 Jul;18(7):433-434. PMID: 28471569.
20: De la Garza-Salazar F, Colunga-Pedraza PR, Gmez-Almaguer D. Cytochrome P450 inhibition to decrease dosage and costs of venetoclax and ibrutinib: A proof-of-concept case study. Br J Clin Pharmacol. 2022 Nov 10. doi: 10.1111/bcp.15590. Epub ahead of print. PMID: 36354135.
21: Fancher KM, Pappacena JJ. Drug interactions with Bruton's tyrosine kinase inhibitors: clinical implications and management. Cancer Chemother Pharmacol. 2020 Oct;86(4):507-515. doi: 10.1007/s00280-020-04137-6. Epub 2020 Sep 17. PMID: 32940733.
22: Mato AR, Ghosh N, Schuster SJ, Lamanna N, Pagel JM, Flinn IW, Barrientos JC, Rai KR, Reeves JA, Cheson BD, Barr PM, Kambhampati S, Lansigan F, Pu JJ, Skarbnik AP, Roeker L, Fonseca GA, Sitlinger A, Hamadeh IS, Dorsey C, LaRatta N, Weissbrot H, Luning Prak ET, Tsao P, Paskalis D, Sportelli P, Miskin HP, Weiss MS, Svoboda J, Brander DM. Phase 2 study of the safety and efficacy of umbralisib in patients with CLL who are intolerant to BTK or PI3K? inhibitor therapy. Blood. 2021 May 20;137(20):2817-2826. doi: 10.1182/blood.2020007376. PMID: 33259589; PMCID: PMC8574211.
23: Krapfl A, McLeod C, Myers R, Venugopal P, Seddon A. Venetoclax ramp-up with concurrent voriconazole in a patient with chronic lymphocytic leukemia. J Oncol Pharm Pract. 2022 Dec;28(8):1898-1901. doi: 10.1177/10781552221082295. Epub 2022 Feb 18. PMID: 35179064.
24: Podoll T, Pearson PG, Kaptein A, Evarts J, de Bruin G, Emmelot-van Hoek M, de Jong A, van Lith B, Sun H, Byard S, Fretland A, Hoogenboom N, Barf T, Slatter JG. Identification and characterization of ACP-5862, the major circulating active metabolite of acalabrutinib: both are potent and selective covalent BTK inhibitors. J Pharmacol Exp Ther. 2022 Oct 30:JPET-AR-2022-001116. doi: 10.1124/jpet.122.001116. Epub ahead of print. PMID: 36310034.
25: Yu J, Zhou Z, Tay-Sontheimer J, Levy RH, Ragueneau-Majlessi I. Risk of Clinically Relevant Pharmacokinetic-Based Drug-Drug Interactions with Drugs Approved by the U.S. Food and Drug Administration Between 2013 and 2016. Drug Metab Dispos. 2018 Jun;46(6):835-845. doi: 10.1124/dmd.117.078691. Epub 2018 Mar 23. PMID: 29572333.