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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?:** Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/castillo_coi_yoda.pdf  
https://yoda.yale.edu/system/files/coi_form_kk.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. 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.
Research Proposal

Project Title
Ibrutinib plus rituximab versus ibrutinib monotherapy in patients with Waldenström macroglobulinemia: A pooled analysis of prospective studies

Narrative Summary:
Waldenström macroglobulinemia (WM) is a rare blood cancer. Current treatment guidelines include ibrutinib and rituximab as well as ibrutinib alone as preferred regimens to treat WM patients, and both regimens are approved by the FDA. However, no formal comparison exists between these two regimens, and a comparative prospective clinical trial is unlikely to be done. We aim at comparing the safety and efficacy of ibrutinib plus rituximab (Arm A of the INNOVATE study) versus ibrutinib alone (Arm C of the INNOVATE plus two separate prospective studies in previously treated and treatment naïve patients). This study can provide valuable comparative information on the treatment of patients with WM.

Scientific Abstract:
Background
Ibrutinib monotherapy (IBR) and ibrutinib in combination and rituximab (IBR-R) are approved by the FDA for the treatment of Waldenstrom macroglobulinemia (WM). However, no comparative data exist evaluating these two approaches.

Objective
To compare and evaluate the safety and efficacy of IBR versus IBR-R in WM.

Study Design
In this study, data from Arm A of the INNOVATE study (IBR-R arm) will be compared against pooled data from Arm C of the INNOVATE study and two phase II studies (NCT02604511; NCT01614821) (IBR arm).

Participants
Participants with MYD88 mutations (with and without CXCR4 mutations) from the INNOVATE study who received IBR-R (Arm A) and IBR (Arm C), and from two phase II studies (NCT02604511 and NCT01614821) will be included.

Main Outcome Measures
The primary outcome measure is progression-free survival (PFS). Secondary outcome measures are the time to response (TTR), time to major response (TTMR), major response rate, rate of very good partial response (VGPR) or better, overall survival (OS), and adverse event profile.

Statistical Analysis
Baseline characteristics will be compared using Chi square, or Fishers exact test. Univariate and multivariate logistic regression models will be fitted for a major response, and VGPR or better. Time to events will be estimated using Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional-hazard regression models for TTR, TTMR, PFS and OS will be fitted. P-values <0.05 will be considered statistically significant. Adverse events and causes of death will be presented descriptively.

Brief Project Background and Statement of Project Significance:
WM is a rare B-cell lymphoproliferative disorder characterized by the uncontrolled accumulation of IgM-producing lymphoplasmacytic lymphoma (LPL) cells that accumulate in the bone marrow and other organs [1]. The clinical course of WM is variable and although patients might experience a survival measured in decades, WM remains
incurable with current therapeutic regimens. Our group identified a recurrent mutation, MYD88 L265P, detected in over 90% of cases with WM [2]. MYD88 L265P supports growth and survival of WM cells through activation of the Bruton Tyrosine Kinase (BTK) pathway. Furthermore, the activation of BTK by mutated MYD88 was abrogated using BTK inhibitors [3]. Another study from our group reported the occurrence of recurrent somatic CXCR4 mutations in approximately 30-40% of WM patients [4]. CXCR4 mutations provide sustained signaling of AKT, ERK and BTK following SDF-1a binding in comparison with wild-type CXCR4, as well increased cell growth and survival of WM cells despite BTK inhibition [5].

Ibrutinib monotherapy, ibrutinib-rituximab, and zanubrutinib monotherapy are the only regimens approved by the US FDA for the treatment of symptomatic patients with WM. The approval of ibrutinib in 2015 was based on the results of a phase II study in 63 previously treated patients in which ibrutinib monotherapy was associated with response rates of 90% and a 5-year PFS rate of 54% [6, 7]. This initial approval was further supported by experience with ibrutinib monotherapy in 30 treatment-naïve patients with WM with response rates up to 100% and a 4-year PFS rate of 76% [8, 9]. The combination of ibrutinib and rituximab was approved in 2018 based on the results of the phase III INNOVATE study in which 150 patients with WM, including treatment naïve and previously treated, were randomized to the combination or rituximab and placebo [10, 11]. The combination of ibrutinib and rituximab showed response rates over 90% with a 4-year PFS rate of 71%, which were statistically higher than rituximab and placebo.

However, whether the addition of rituximab to ibrutinib is associated with superior outcomes than ibrutinib monotherapy is currently unclear and unlikely to be evaluated in future clinical trials. Furthermore, response rate and PFS to ibrutinib monotherapy were inferior in patients whose malignant cells harbored CXCR4 mutations. In the INNOVATE study, the addition of rituximab to ibrutinib appeared to induce faster responses and longer PFS than expected with ibrutinib monotherapy. It is possible that the addition of rituximab might positively impact the effect of ibrutinib in WM patients with CXCR4 mutations. Finally, it is also possible that the addition of rituximab might be associated with unique adverse events in WM patients.

Based on the above, the present study will provide additional, previously unexplored information on the comparative safety and efficacy of IBR versus IBR-R and could directly impact the future management of patients with WM.

Specific Aims of the Project:

The primary objective of this study is to compare the PFS distribution between the IBR-R and the IRB arms.

Secondary objectives include comparing the distribution of TTR, TTMR, and overall survival (OS), and the proportion of overall response (ORR; minor response or better), major response (partial response [PR] or better), and very good PR (VGPR) or better, and adverse event profile between arms.

What is the purpose of the analysis being proposed? Please select all that apply.
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

Data will be collected from three prospective studies:
• NCT02165397 (INNOVATE trial, arms A and C – requested data)
• NCT02604511 (ibrutinib in previously untreated WM – available data; Treon et al. J Clin Oncol 2021)
• NCT01614821 (ibrutinib in previously treated WM – available data; Castillo et al. Leukemia 2022)
Data from NCT02604511 and NCT01614821 are available to me, as I am a co-investigator for these two investigator-initiated studies. The analysis will be run in the platform provided by YODA, which will be accessed via an encrypted, password-protected laptop or a password-protected computer located in the investigator's key-locked office.

Inclusion criteria
• Participants exposed to IBR with or without rituximab in any of the three prospective studies above.
Exclusion criteria
• MYD88 wildtype mutational status

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

The main outcome of the study will be PFS, defined as the time from treatment initiation to disease progression, death or last follow-up visit.

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

The main predictor of this study will be the treatment regimen, which will be divided into two groups:
• IBR-R group
• IBR group

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

Baseline categorical variables of interest include:

• Age (>65 and ?65 years)
• Sex (male and female)
• Serum IgM level (?4,000 and <4,000 mg/dl)
• Serum IgM level (?7,000 and <7,000 mg/dl)
• Hemoglobin level (<11.5 and ?11.5 g/dl)
• Platelet count (?100 and >100 K/uL)
• Serum beta-2 microglobulin (>3 and ?3 mg/L)
• Albumin (<3.5 g/dl and >3.5 g/dl)
• IPSSWM score (low, intermediate, high)
• Bone marrow involvement (?60% and <60%)
• CXCR4 mutational status (mutated and wildtype)
• Treatment status (treatment naïve and previously treated)

Other outcomes of interest include:

• Minor response rate (?25% but <50% decrease in baseline serum IgM)
• PR rate (?50% but <90% decrease in baseline serum IgM)
• VGPR rate (?90% decrease in baseline serum IgM, or normalization in serum IgM with persistence of monoclonal spike in serum electrophoresis)
• Complete response rate (normalization of serum IgM, serum electrophoresis, extramedullary disease and bone marrow)
• Median TTR and TTMR.
• 2-year and 4-year PFS rate
• 2- and 4-year OS rates
• Adverse events
• Cause of death

Statistical Analysis Plan:

Clinicopathological characteristics will be dichotomized and reported using descriptive statistics. Clinicopathological characteristics between groups will be compared using the Chi square (if categorical and >10 events per subgroup) or the Fishers exact test (if categorical and <10 events per subgroup).

Univariate logistic regression models will be fitted separately for major response rate and rate of VGPR or better. The dependent variables will be age (>65, <65 years), serum IgM level (>4,000, <4.000 mg/dl), hemoglobin level (>11.5 g/dl, <11.5 g/dl), platelet count (?100 K/uL, >100 K/uL), serum beta-2-microglobulin level (>3 mg/L, <3 mg/L), serum albumin level (<3.5 g/dl, ?3.5 g/dl), International Prognostic Scoring System for WM (IPSSWM; low, intermediate, high), bone marrow involvement (?60%, <60%), treatment status at baseline (treatment naïve, previously treated), and CXCR4 mutational status (mutated, wildtype). Variables associated with p<0.1 will be
included in the multivariate analysis. The International Prognostic Scoring System for WM (IPSSWM) score [12]
(low, intermediate, high), and the ibrutinib PFS risk score [13] (low, intermediate, high) will also be evaluated but
will not be included in the multivariate analysis.

Time to event distribution for TTR, TTMR, PFS and OS will be estimated using the Kaplan-Meier method, and
comparison between distributions will be assessed using the log-rank test. Univariate Cox proportional-hazard
regression models will be fitted separately for TTR, TTMR, PFS and OS. The dependent variables will be age (?65,
<65 years), serum IgM level (?4,000, <4,000 mg/dl), hemoglobin level (?11.5 g/dl, <11.5 g/dl), platelet count (?100
K/UL, <100 K/UL), serum beta-2-microglobulin level (?3, <3 mg/l), serum albumin level (<3.5 g/dl, ?3.5 g/dl), bone
marrow involvement (?60%, <60%), treatment status at baseline (treatment naive, previously treated), and CXCR4
mutational status (mutated, wildtype). Variables associated with p<0.1 will be included in the multivariate analysis.
The International Prognostic Scoring System for WM (IPSSWM) score (low, intermediate, high), and the ibrutinib
PFS risk score (low, intermediate, high) will also be evaluated but will not be included in the multivariate analysis.

In the multivariate logistic and Cox regression analyses, variables associated with p<0.05 will be considered
statistically significant.

Adverse events and causes of death will be presented descriptively. No statistical comparisons will be performed
for adverse events of causes of death.

Software Used:
STATA

Project Timeline:

Once data are acquired, three months will be required to perform the analysis, and three additional months will be
needed to generate abstracts and a final manuscript.

Dissemination Plan:

Abstracts will be submitted to the Annual Meetings of the European Haematology Association or the American
Society of Hematology, whenever appropriate. A final manuscript will be submitted to Blood (Impact factor 23
[Clarivate, 2020]).

Bibliography:

1. Swerdlow SH, Cook JR, Sohani AR, Pileri SA, Harris NL, Jaffe ES, et al, Lymphoplasmacytic lymphoma, in
WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues, S.H. Swerdlow, et al., Editors. 2017,
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macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small
promote ibrutinib resistance but do not supplant MYD88(L265P) -directed survival signalling in Waldenstrom
565-575.
Versus Placebo Plus Rituximab for Waldenstrom's Macroglobulinemia: Final Analysis From the Randomized Phase