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How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/schjesvold_coi_-_predictive.pdf
https://yoda.yale.edu/system/files/alvaro_coi.pdf
https://yoda.yale.edu/system/files/arnolod_coi.pdf
https://yoda.yale.edu/system/files/coi_yoda_kevin_leder.pdf
https://yoda.yale.edu/system/files/conflictofinterestevenmyklebust.pdf
https://yoda.yale.edu/system/files/foo_coi.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. NCT03180736 - 54767414MMY3013 - A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor

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

Research Proposal

Project Title

Personalized prediction of PFS in myeloma patients treated with DaraPomDex or Pom-Dex alone, using combined machine learning and mechanistic modeling

Narrative Summary:

Myeloma remains largely incurable. The disease is marked by recurrent episodes of relapses that are difficult to predict. This project utilizes patient characteristics, treatment history and measurements obtained under MM treatment in a phase III daratumumab clinical trial to develop computational tools able to predict treatment relapses in individual patients. To create predictions from this data, machine learning and mathematical modeling techniques will be utilized together. The resulting algorithm will be used to predict clinical outcomes of future patients treated with the therapies used in the clinical trial, and may assist in the design of future personalized treatment strategies.

Scientific Abstract:

Background:
Personalized treatment guidelines for relapsed and refractory (RR)MM patients are limited to the investigation of translocation t(11,14) to decide about venetoclax-based regimes. MM remains largely incurable, and the disease is typically marked by recurrent episodes of remission and relapse that are difficult to predict.
Objective:
To develop and validate a statistical model able to provide personalized prediction of Progression Free Survival (PFS) in RRMM patients treated with daratumumab plus pomalidomide and dexamethasone or pomalidomide and dexamethasone alone.
Study Design
Retrospective analysis using data from a two-arm Randomized Controlled Trial.
Subjects diagnosed with RRMM who participated in the Phase III randomized trial NCT03180736.
Primary and Secondary Outcome Measures:
PFS
Statistical Analysis

This is a post-hoc analysis of NCT03180736 assessing the possibility of predicting FS using state-of-the-art statistical methods. We will use a hierarchical Bayesian modeling framework that couples a mechanistic model of treatment response with a selection of machine learning models. Specifically, longitudinal M-protein measurements will be modeled with a non-linear mechanistic model accounting for sensitive and resistant cancer populations. Machine learning models will then couple baseline data and longitudinal measurements with the parameters of the mechanistic model, balancing group-level learning with patient-specific accuracy through mixed effect modeling. Patients in each trial arm will be divided in balanced train and test groups, and 10-fold cross validation will be used in training to ensure generalizability of the method. We will perform Bayesian inference using Hamiltonian Monte Carlo methods on the train group and evaluate the model performance on the test group.

Brief Project Background and Statement of Project Significance:

Introduction of new treatments for multiple myeloma (MM) has pushed median patient survival to approximately 6 years. However, MM patients and their corresponding clinical outcomes are very heterogeneous. While some patients experience long remission periods, others are refractory to therapy or have an early relapse. The disease course is typically marked by recurrent episodes of remission and relapse that are currently difficult to predict on individual patient level. After relapse, selection of next treatment lines, usually composed of two or three drugs, is mainly based on group-level scientific evidence, on the clinician's experience and some trial-and-error. Despite many advances in the use of molecular technologies to characterize MM, current personalized treatment guidelines are limited to the investigation of translocation t(11,14) to decide venetoclax-based regimes in relapse and refractory patients (Dimopoulos et al., HemaSphere, 2021).
Our aim is to develop and validate statistical learning tools for predicting progression-free survival times for individual MM patients. These tools utilize both individual patient characteristics, treatment histories, as well as learned response patterns across a large cohort of patients, and they will enable the design of personalized treatment strategies. In preliminary work we have developed a novel Hierarchical Bayesian model that combines a mechanistic model of treatment response with machine learning to predict patient response to therapies. Drawing from a cohort of patients exposed to a given treatment A, our method learns which factors in the clinical history of each patient - including previous treatments, genetic markers or clinical and demographic variables - predict the patient's response to treatment A, with the uncertainty of the estimate quantified by the Hierarchical Bayesian framework. Once trained on a clinical data set, it will enable personalized prediction of how patients will respond to treatment A, given their clinical history and previous responses to other treatments. If performed for a suite of available therapies, this method will provide insights into the preferable next course of therapy for individual patients.
To train and validate our approach, we seek high-quality treatment response data from recent MM clinical trials for therapies currently in use. Rapid introduction of new treatments means that algorithms for treatment recommendations must be trained on recent data to be of clinical relevance. Daratumumab, a monoclonal antibody against CD38, was approved in 2015 in the US and in 2017 in the EU for the treatment of MM patients who have received at least three prior therapies including a PI and an IMiD, or who are double refractory to these drugs. While efficacy in these RRMM patient population have been demonstrated (Dimopoulos et al., The Lancet Oncology, 2021), response heterogeneity is commonly observed. Thus, identifying the patients that can better benefit from the addition of this drug is an unmet medical need.

Specific Aims of the Project:

Project aim: Develop and validate statistical and computational frameworks combining mathematical modeling with machine learning to predict patient-specific PFS.
Building upon our existing hierarchical Bayesian framework, we will use a mechanistic model for response to pomalidomide and dexamethasone with or without daratumumab and train different machine learning models to predict response parameters from patient characteristics and clinical histories. We will train and validate the models on data from NCT03180736 and assess their ability to predict patient-specific PFS. This framework can then be used to generate treatment response predictions and recommendations.
The specific hypothesis that is tested is whether state-of-the-art Bayesian nonlinear models for repeated measurement data (Lee, 2022) are able to predict PFS in RRMM patients using the information available before treatment start.

What is your Study Design?:

Individual trial analysis

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

Develop or refine statistical methods

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:

Individual patient-level data from NCT03180736 – Phase 3 study comparing Pomalidomide and Dexamethasone with or without Daratumumab in subjects with relapsed or refractory multiple myeloma who have received at least one prior line of therapy with both Lenalidomide and a proteosome inhibitor.
We will include in our analysis only patients that were followed by serum monoclonal component. For those patients, we request all available demographic, clinical and laboratory variables specified in Study Schedule section 7.2 and table 7.3 of the study protocol.

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

The main outcome measure is PFS. Bayes factors will be used to compare prediction models, and the PFS prediction accuracy on train and test data will be quantified by mean square error to provide a more interpretable metric.
In addition, as secondary outcome, we classify patients into responders and non-responders to treatment. We define responders as patients who have a reduction of at least 50% in the tumor load, as observed via M-protein measurements.
Framing the secondary outcome as a classification task enables the use of binary classification measures like sensitivity and specificity, precision and recall, and the Area Under The Receiver Operator curve, accuracy measures that are easy to interpret clinically.

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

We use M-protein to characterize disease progression assuming it is proportional to tumor burden. We describe M-protein dynamics as a function of response parameters: fraction of the resistant population; growth rates of resistant and sensitive populations under treatment. In turn, machine learning models describe response parameters as a function of all available demographic, clinical and laboratory variables in a framework of penalized variable selection.

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

We will use available genetic markers and will compare predictive performance achieved by using all available markers compared to using a subset of markers that have been identified as risk factors (Rustad et al., 2020).
In addition, to the degree it is available, we can incorporate the patient's prior history, which by definition is a complex multivariate time series. To include this in our model, feature extraction methods can be applied to relevant historical time series variables, and the extracted features will be used as covariates.

Statistical Analysis Plan:

We will use a hierarchical Bayesian model that is specified in "Hierarchical_Bayesian_model.pdf"., where observations refer to longitudinal M-protein measurements and covariates are demographic, clinical and laboratory variables at baseline. The mechanistic model of the M-protein will be coupled with a selection of machine learning models such as random forests and neural nets, which are able to capture interactions and nonlinearities in the dependency of the treatment response on the covariates. We will generalize this framework to account for time-dependent covariates, so that we can incorporate in the analysis the covariate measurements under treatment. We will perform Bayesian inference using gradient-based algorithms for Markov chain Monte Carlo (MCMC) sampling,

known as Hamiltonian Monte Carlo, implemented in PyMC.
The separate machine learning methods will be compared in terms of their ability to explain the observed data via Bayes factors.
Software Used:
Python
Project Timeline:

Completion is estimated within 12 months of data availability. In months 1-8 we will develop and validate the computational framework to predict patient-specific progression-free survival times in response to the treatment combinations. At this point we will begin writing a manuscript on the novel approach that we plan to submit to a methodological journal by month 10. During months 9-12 we will use the validated computational framework to identify treatment response biomarkers for each treatment arm and generate response predictions for individual MM patients. A manuscript on findings specific to multiple myeloma and the treatments considered in these datasets will be drafted from month 12.

Dissemination Plan:

Results from this study will be used to inform predictions of clinical outcomes from individual treatment responses. The model, computational code and results will be published and made available to the community. If our method achieves a sensitivity and specificity of treatment response that are both above 80 %, we will consider the precision good enough to be of special clinical interest, and will prioritize publication in high-ranking clinically oriented journals. The results will also be presented at international conferences in biostatistics and cancer. Finally, we will consider options for collaborating with pharmaceutical companies to develop our method into a tool for clinical practice.

Bibliography:

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