**Research Proposal**

**Project Title**

Identifying Prognostic and Predictive Factors for Causal Dose-Response Analysis of Daratumumab in Multiple Myeloma

**Scientific Abstract**

Dose optimization has become a pivotal component of oncology drug development. In clinical trials, Dose-Response (D-R) analyses serve as an essential step to support dose selection. Nevertheless, it’s challenging to derive a causal D-R relationship due to the presence of heterogeneous treatment effects (HTE)1. To achieve a better understanding of causal D-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 D-R relationships. In this study, we aim to evaluate the D-R relationship of daratumumab in treatment of multiple myeloma (MM) 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 D-R relationship of daratumumab based on subgroup analysis.

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

Multiple myeloma (MM) has risen as a growing global concern, with several targeted therapies developed, including the innovative CD38-targeting antibody, daratumumab. Daratumumab has shown remarkable efficacy and safety in both monotherapy and combination regimens for MM patients. Certain reports have indicated that daratumumab may exhibit dose-dependent efficacy and dose-dependent toxicity2,3. This underscores the significance of meticulously determining an optimal dosage that effectively manages the delicate equilibrium between therapeutic benefits and potential risks. One common way is to perform dose-response (D-R) analyses. However, multiple confounding factors can affect patient response, making it difficult to apply average D-R relationships to address questions concerning dose optimization. Heterogeneous treatment effects (HTE) analyses can help identify critical confounding factors and elucidate causal D-R relationships. Using daratumumab as an example, this study aims at elucidating how the D-R relationships are shaped by different prognosis or risk levels and deriving causal D-R relationships for 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 a causal D-R relationship of daratumumab in treatment of MM. This study is proposed with two specific aims:

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

Aim 2: To derive a causal D-R relationship for daratumumab in treatment of MM by untangling confounding effects.

**Study Design**

This study will assemble the clinical data of MM patients receiving daratumumab and relevant agents. HTE analyses will be performed to identify potential prognostic and predictive factors that influence MM patient response and survival. Several strategies, including conventional subgroup HTE approach, risk-based HTE approach, and effect-based HTE approach4, will be employed to subgroup patients and evaluate treatment effects. The D-R relationship of daratumumab 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 daratumumab, if any, are also desirable.

**Purpose of Analysis**

This study seeks to identify critical prognostic and predictive factors affecting MM patient response and survival outcomes and derive causal D-R relationships of daratumumab in treatment of MM.

**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 subgroups.
5. Derive casual D-R relationships: Evaluate the relationship between daratumumab dose/exposure and patient response within each subgroup.

**Software to be used**

R and Monolix

**Data Source and Inclusion/Exclusion Criteria**

Adult patients receiving daratumumab and/or other relevant agents for the treatment of multiple myeloma from studies NCT01615029, NCT00574288, NCT03277105, NCT03412565, and NCT01998971. 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, extramedullary plasmacytoma, proportion of plasma cells in bone marrow, International Staging System (ISS) class, etc.
3. Treatment-related variables: dosage, dosing schedule, duration of treatment, concomitant medications, etc.
4. Outcome measure: patient response based on International Myeloma Working Group (IMWG) criteria, Time to progression (TTP), duration of response, progression-free survival (PFS), overall survival (OS), etc.
5. PK data: daratumumab concentration-time profile.

**Primary Outcome Measure**

Patient response based on International Myeloma Working Group (IMWG) criteria

**Secondary Outcome Measure**

Time to progression (TTP), duration of response, progression-free survival (PFS), overall survival (OS), side effects.

**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, extramedullary plasmacytoma, proportion of plasma cells in bone marrow, International Staging System (ISS) class, etc.

Treatment-related variables: dose, dosing frequency, duration of treatment, concomitant medications, etc.

**Other Variables of Interest**

Therapeutic exposure: daratumumab dosage, individual concentration-time profiles of daratumumab

**Statistical Analysis Plan**

The statistical analysis plan for this research project is designed to rigorously evaluate the dose-response relationship of daratumumab in treatment of multiple myeloma. 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 daratumumab concentrations. We will also examine the distribution of patient response outcomes based on the IMWG criteria and secondary endpoints such as Time to Progression (TTP), Duration of Response, Progression-Free Survival (PFS), and Overall Survival (OS) to gain a preliminary understanding of the data.

Population Pharmacokinetics (popPK) Model: To understand the pharmacokinetic behavior of daratumumab in individual patients, a population pharmacokinetics (popPK) model which accounts for multiple covariates will be employed to characterize the concentration-time profiles of daratumumab 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 daratumumab within defined subgroups. Logistic regression analyses will be employed to evaluate the relationship between daratumumab dose/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.

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3. Lokhorst HM, Laubach J, Nahi H, et al. Dose-dependent efficacy of daratumumab (DARA) as monotherapy in patients with relapsed or refractory multiple myeloma (RR MM). *JCO*. 2014;32(15\_suppl):8513-8513.

4. 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.