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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-Cao1.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.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. NCT01615029 - An Open Label, International, Multicenter, Dose Escalating Phase I/II Trial Investigating the Safety of Daratumumab in Combination With Lenalidomide and Dexamethasone in Patients With Relapsed or Relapsed and Refractory Multiple Myeloma

2. [NCT03277105 - A Phase 3 Randomized, Multicenter Study of Subcutaneous vs. Intravenous Administration of Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma](#)
3. [NCT00574288 - Daratumumab (HuMax®-CD38) Safety Study in Multiple Myeloma - Open Label, Dose-escalation Followed by Open Label, Single-arm Study](#)
4. [NCT03412565 - A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination With Standard Multiple Myeloma Treatment Regimens](#)
5. [NCT01998971 - An Open-Label, Multicenter, Phase 1b Study of JNJ-54767414 (HuMax CD38) (Anti-CD38 Monoclonal Antibody) in Combination With Backbone Regimens for the Treatment of Subjects With Multiple Myeloma](#)

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 Dose-Response Analysis of Daratumumab in Multiple Myeloma

Narrative Summary:

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.

Scientific Abstract:

Background: 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.
Objective: 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.
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 approach2, will be

employed to subgroup patients and evaluate treatment effects. The D-R relationship of daratumumab will be analyzed within subgroups.

Participants: Adult patients receiving daratumumab and/or other relevant agents for the treatment of multiple myeloma from studies NCT01615029, NCT00574288, NCT03277105, NCT03412565, and NCT01998971.

Primary and Secondary Outcome Measure(s): The primary outcome measure is patient response based on International Myeloma Working Group (IMWG) criteria. 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 daratumumab for each individual. THE analyses will be employed to subgroup patients based on risk prediction model or effect model. D-R analyses will be performed for each subgroup.

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:

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 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:

Adult patients receiving daratumumab and/or other relevant agents for the treatment of multiple myeloma from studies NCT01615029, NCT00574288, NCT03277105, NCT03412565, and NCT01998971. Inclusion criteria: (1) Patients must be 18 Years and older (Adult, Older Adult); (2) Patients have been diagnosed with multiple myeloma; (3) Patients have received daratumumab for treatment of multiple myeloma.
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 and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary Outcome Measure
Patient response based on International Myeloma Working Group (IMWG) criteria5.
The International Myeloma Working Group (IMWG) criteria categorize patient response to therapy into different groups5:
1. Complete response (CR): Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and less than (<) 5 percentage (%) plasma cells in bone marrow.
2. Stringent complete response (sCR): CR+Normal free light chain ratio and absence of clonal cells in bone marrow by immunohistochemistry or immune fluorescence.
3. Partial response (PR): greater than equal to (>=) 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >= 90 percentage (%) or to <200 mg/24 hours.
4. Very good partial response (VGPR): Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hour.
5. Progressive disease (PD): Increase of > 25% from lowest response value in any one or more of the following:
a. Serum M-component and/or (the absolute increase must be > 0.5 g/dL).
b. Urine M-component and/or (the absolute increase must be > 200 mg/24 h).
c. Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL.
d. Bone marrow plasma cell percentage: the absolute percentage must be > 10%;
e. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
f. Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.
6. Stable disease (SD): Not meeting criteria for CR, VGPR, PR, or progressive disease.

Secondary Outcome Measures
The secondary outcome measures include:
1. Time to progression (TTP): TTP was defined as the number of days from the date of first infusion (Day 1) to the date of first record of disease progression.
2. Duration of response (DOR): DOR was calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease.
3. Progression-free survival (PFS): PFS was defined as the time between the date of first dose of daratumumab and either disease progression or death, whichever occurs first.
4. Overall survival (OS): OS was defined as the number of days from administration of the first

infusion (Day 1) to date of death.

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

The main predictor is the exposure of daratumumab, which includes:
1. Daratumumab Dosage: This refers to the specific quantity of daratumumab prescribed to each patient.
2. Timing of Administration: The precise schedule and timing at which daratumumab is administered to patients.
3. Daratumumab Concentration-Time Profiles: This factor involves monitoring and analyzing the concentration of daratumumab 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.
• etc.
Disease-related variables:
• Time Since Diagnosis: The period that has elapsed from the time a patient was initially diagnosed with multiple myeloma, typically measured in years or months.
• Extramedullary Plasmacytoma: An extramedullary plasmacytoma is a rare form of plasma cell neoplasm in which abnormal plasma cells, also known as myeloma cells, develop outside the bone marrow, often in soft tissues or organs.
• Proportion of Plasma Cells in Bone Marrow: This variable represents the percentage of plasma cells within the patient's bone marrow, which is a critical factor in diagnosing and monitoring conditions like multiple myeloma.
• International Staging System (ISS) Class: The International Staging System is a classification system used primarily for multiple myeloma patients to categorize the disease's stage and prognosis. It divides patients into three classes based on the levels of two blood proteins: beta-2 microglobulin and albumin.
• etc.
Treatment-related variables:
• Concomitant medications: Concomitant medications refer to any additional drugs or therapies that a patient is prescribed or receiving alongside daratumumab.

Statistical Analysis Plan:

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.

Software Used:

R

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:

This work will primarily be disseminated through publications and presentations, such as Clinical Pharmacology & Therapeutics, Cancer Research, or Journal for ImmunoTherapy of Cancer. The analyses aim to identify the key prognostic and predictive factors for treating MM. 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:

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.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2023/10/Research_Proposal_Daratumumab_Cao-at-UNC.docx