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General Information

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SCOPUS ID:
Requires Data Access? No

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?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/05/index.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/SV_57KskaKADT3U9Aq-R_4TLz2vWrmNlw4Xk.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 - 54767414GEN503 - 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. NCT02951819 - 54767414MMY2012 - Daratumumab Plus Cyclophosphamide, Bortezomib and Dexamethasone (Dara-CyBorD) in Previously Untreated and Relapsed Subjects With Multiple Myeloma
3. 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
4. NCT01985126 - 54767414MMY2002 - An Open-label, Multicenter, Phase 2 Trial Investigating

the Efficacy and Safety of Daratumumab in Subjects With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy (Including a Proteasome Inhibitor and IMiD) or Are Double Refractory to a Proteasome Inhibitor and an IMiD

5. NCT02136134 - 54767414MMY3004 - Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects With Relapsed or Refractory 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

Predicting Treatment Response to Daratumumab in patients with Relapsed or Refractory multiple myeloma

Narrative Summary:

Daratumumab is approved as monotherapy for relapsed or refractory multiple myeloma (RRMM) and in combination with standard-of-care regimens for patients with RRMM and has shown promising effects. However, some patients have shown resistance to daratumumab.In this study we will investigate clinical and genetic features that predict favorable response to Daratumumab, and to build a novel signature of candidate biomarkers for good response to Dara.

Scientific Abstract:

Background:Multiple myeloma (MM) is a hematological cancer characterized by abnormal proliferation of plasma cells in bone marrow. The prognosis of MM is highly heterogeneous due to the molecular differences between patients.
Objective:To identify features (e.g., age, gender, gene biomarkers)that predict a favorable response to Daratumuban in patients with with RRMM,in the form of a nomogram.
Study Design:This is a post hoc analysis including clinical trials in RRMM patients. Biomarkers like age,gender,ISS,R-ISS, serum β2-microglobulin, albumin, LDH,gene biomarkers and MRD status will be evelauted.This study will build a novel signature of candidate biomarkers for good response to Dara.
Participants: Patients with RRMM receiving Dara-based regimens.
Main Outcome Measure(s): The primary outcome is PFS.The second outcomes include OS and DOR.
Statistical Analysis:
Logistic and cox regression will be used to assess the relationship between candidate biomarkers and survival outcomes, after adjusting for confounders..candidate biomarkers were selected to further construct a nomogram for predicting prognosis.

Brief Project Background and Statement of Project Significance:

Multiple myeloma (MM) is a hematological cancer characterized by abnormal proliferation of plasma cells in bone marrow(1). The prognosis of MM is highly heterogeneous due to the molecular differences between patients. Although some new drugs and regimens have improved therapeutic efficacy there are still many patients ultimately dying from disease progression. Increased understanding of the microenvironmental interactions between malignant plasma cells and the bone marrow niche, and their role in disease progression and acquisition of therapy resistance, has helped develop new drugs and regimens.Daratumumab is a human immunoglobulin Gk monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action(2.Daratumumab is approved as monotherapy for relapsed

or refractory MM (RRMM) and in combination with standard-of-care regimens for patients with RRMM or NDMM.
In pre-Dara era established prognostic models such as the International Staging System (ISS) and the Revised ISS (R-ISS), incorporating genetic features alongside clinical parameters such as serum β2-microglobulin, albumin, and lactate dehydrogenase (LDH), have enabled risk stratification and informed treatment decisions.However, whether these prognostic signatures can be applied to predict the efficacy of daratumumab remains unknown.
This study will investigate the associations between outcomes and characteristics (e.g., age, gender, gene biomarkers)of patients with RRMM treated with daratumumab and build a model that can be to select patients who will derive the greatest potential benefit from daratumumab.

Specific Aims of the Project:

The primary aim of this analysis was to develop and validate a prognostic model based on readily available,routinely collected clinical and laboratory data to predict survival outcomes in relapsed or refractory myeloma patients with daratumumab.

Study Design:

Individual trial analysis

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

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

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:

Inclusion:Patients with RRMM receiving Dara. Males and females at least 18 years of age.Must have had documented replased and refractory multiple myeloma.Must have received at least 1 prior line of therapy for multiple myeloma.Must have an Eastern Cooperative Oncology Group Performance Status score of 0, 1, or 2.Must have had documented evidence of progressive disease as defined based on Investigator's determination of response of International Myeloma Working Group (IMWG) criteria on or after their last regimen.
Exclusion:Patients crossed over to the other group.

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

Progression Free Survival (PFS): duration from date of first dose (start of induction) to date of first documented evidence of progressive disease (PD) based on computerized algorithm per IMWG criteria or death due to any cause, whichever occurred first.
Overall Survival (OS):the number of days from administration of the first infusion (Day 1) to date of death.
Duration of Response(DOR):the time from the date of initial documented response to the date of first documented evidence of progressive disease (PD) or death due to PD.
ORR:The Overall response rate was defined as the percentage of participants who achieved stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) according to the International Myeloma Working Group (IMWG) criteria, during the study or during follow up.

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

study:

Demographics: Age, Sex, Body Mass Index
MM related features: DS stage ISS, R-ISS
Labs:M protein classification,M protein quantification,proportion of light chains, β2-microglobulin (B2M), albumin, and LDH, gene markers,FISH
Concomitant therapy

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

Other variables of interest include potential biomarkers, such as c-reactive protein,haemoglobin, neutrophils, lymphocytes, platelet and so on, previous treatments

Statistical Analysis Plan:

Continuous variables were summarized as mean (standard deviation) or median (range), and categorical variables were summarized as frequency (%). The difference of continuous measurements was examined using the t-test. The association between categorical variables was examined using the chi-square test. PFS and OS were calculated using the Kaplan–Meier method; Log-rank tests were performed to test for significance at a two-sided alpha-level of 0.05 and Cox models were used to estimate and construct 95% confidence intervals for the HR.For the subgroup analysis, HRs of duration of response (DOR) were calculated for prespecified subgroups using Cox models. In the univariate analysis, prespecified variables were tested for associations with the time of first response using Cox regression models; variables with p < 0.05 in the univariate analysis were selected for multivariable analysis.ndependent factors were selected to further construct a nomogram for predicting prognosis. All tests were two-sided and pvalues 0.05 were considered statistically significant.

Software Used:

R

Project Timeline:

Anticipated project start date:September 1, 2024
Analysis completion date: December 1, 2024
Date manuscript drafted: March 1, 2025
Date manuscript first submitted for publication: May1, 2025

Dissemination Plan:

We anticipate generating one manuscript from the project. The target audience will be hematologists who treat multiple myeloma patients.

Bibliography:

[1]Rollig, C., Knop, S., & Bornhauser, M. (2015). Multiple myeloma. Lancet, 385(9983), 2197-2208. doi:10.1016/S0140-6736(14)60493-1
[2]Kim, K., & Phelps, M. A. (2023). Clinical Pharmacokinetics and Pharmacodynamics of Daratumumab. Clin Pharmacokinet, 62(6), 789-806. doi:10.1007/s40262-023-01240-8