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General Information

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?: Thomson Reuters

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/03/SV_57KskaKADT3U9Aq-R_3dheLZ4dVfIFyXT.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. NCT02252172 - 54767414MMY3008 - A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High Dose Therapy
2. NCT02195479 - 54767414MMY3007 - A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (D-VMP), in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High-dose Therapy

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

Research Proposal

Project Title

Comparative Outcomes of DVMP, DRd, VMP, and Rd in Older High-Risk Cytogenetic Multiple Myeloma Patients: A Propensity Score Analysis

Narrative Summary:

Multiple myeloma is a blood cancer that mainly affects older adults. Some patients have high-risk genetic changes that make the disease more aggressive and lead to worse outcomes. It remains unclear which treatment works best for these high-risk patients, especially when they cannot have a stem cell transplant. Our study will combine patient data from two major trials (ALCYONE and MAIA) to compare four treatment options. Using advanced matching methods, we will determine which therapy best extends life and controls the disease, ultimately improving care.

Scientific Abstract:

Background: Multiple myeloma (MM) primarily affects older adults, many of whom cannot undergo stem-cell transplants. High-risk cytogenetic abnormalities (e.g., del(17p), t(4;14), t(14;16)) lead to more aggressive disease. Although trials like ALCYONE (DVMP vs. VMP) and MAIA (DRd vs. Rd) have shown the benefits of daratumumab-based regimens, few studies directly compare treatments in high-risk patients.
Objective: To compare the efficacy and safety of four frontline regimens--DVMP, VMP, DRd, and Rd--in transplant-ineligible patients aged >=65 with newly diagnosed MM and high-risk cytogenetics.
Study Design: We will perform a pooled retrospective analysis of patient-level data from the ALCYONE and MAIA trials. Only patients with high-risk cytogenetics who received treatment will be included. Propensity score matching will balance baseline factors, allowing us to compare progression-free survival (PFS), overall survival (OS), response rates, and toxicity profiles.
Participants: Patients aged >=65, deemed transplant-ineligible per trial criteria, with high-risk cytogenetics and complete baseline data.
Outcome Measures: Primary: PFS. Secondary: OS, depth of response (e.g., complete response or better), and safety (grade >=3 infections, hematologic toxicities, peripheral neuropathy).
Statistical Analysis: Propensity scores will be generated via logistic regression to adjust for key variables. Time-to-event outcomes will be analyzed with Kaplan--Meier curves and log-rank tests, with hazard ratios from Cox models. Logistic regression will assess response and safety endpoints.

Brief Project Background and Statement of Project Significance:

Multiple myeloma (MM) is characterized by malignant proliferation of clonal plasma cells and often presents in older individuals. Patients with high-risk cytogenetics, including del(17p) and translocations t(4;14) or t(14;16), generally exhibit a more aggressive disease course and inferior outcomes [1,2]. Although newer regimens that incorporate daratumumab--such as DVMP and DRd--have notably extended survival in heterogeneous patient populations, the specific impact of these regimens relative to standard, non-daratumumab comparators (VMP, Rd) in high-risk patients remains understudied [3,4].

The phase 3 MAIA trial demonstrated superior progression-free survival (PFS) with DRd compared to Rd in transplant-ineligible patients [4], while the phase 3 ALCYONE trial showed improved overall survival (OS) with DVMP vs. VMP [3]. However, both trials enrolled patients with variable cytogenetic risk profiles, and they did not directly compare all four regimens in the high-risk subset.

By consolidating individual participant data from these two landmark trials, our study will isolate patients with high-risk cytogenetics and systematically evaluate the relative benefits and safety of DVMP, VMP, DRd, and Rd. This project is highly significant in that it examines a pressing clinical question--whether more intensive or daratumumab-based regimens offer substantial advantages over standard therapies in a subgroup that often experiences early relapse and poor prognosis. We anticipate that our results will inform risk-adapted therapeutic strategies and may influence future consensus guidelines for high-risk MM.

Specific Aims of the Project:

Objective 1: Compare progression-free survival (PFS) across four frontline regimens--DVMP, VMP, DRd, and Rd--among older (>=65 years) transplant-ineligible patients with high-risk cytogenetics. To determine whether incorporating daratumumab (DVMP or DRd) or intensifying therapy with

bortezomib/melphalan (DVMP, VMP) confers improved PFS in the high-risk setting.

Objective 2: Evaluate overall survival (OS) and depth of response (e.g., rate of CR or better, minimal residual disease [MRD] negativity if available) in the same high-risk cohort. To determine whether enhanced initial disease control correlates with a significant OS benefit and higher-quality remissions.

Objective 3: Characterize the safety profile of these regimens by comparing the incidence of grade >=3 adverse events--particularly infections, hematologic toxicities, and peripheral neuropathy--among high-risk cytogenetic patients. To assess whether more intensive regimens introduce an unacceptable burden of toxicity in a population already at higher risk of complications.

Study Design:

Other

Study Design Explanation:

Although the analysis will draw on data from two distinct phase 3 trials (ALCYONE and MAIA), this is not a conventional meta-analysis of published summaries. Instead, it constitutes a pooled individual patient data (IPD) study, integrating raw de-identified data from both trials into a unified dataset. We will subsequently use propensity score matching to balance baseline characteristics across four distinct treatment arms (DVMP, VMP, DRd, Rd) within the high-risk subgroup. This approach enhances causal inference by reducing confounding, thereby providing more robust and clinically relevant comparisons than those typically generated by standard meta-analytic methods.

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research Methods

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

We will use de-identified individual-level data from the ALCYONE and MAIA phase 3 trials accessed through the YODA Project's secure platform.

Inclusion Criteria
Confirmed diagnosis of MM.
Age >=65 years.
High-risk cytogenetic features.
Not eligible for stem-cell transplantation as per the original trial protocols.
Complete baseline data for the relevant covariates used in propensity score matching.

Exclusion Criteria
Standard-risk or intermediate-risk patients lacking high-risk cytogenetic features.
Missing or incomplete baseline data for key matching variables.
Patients who did not receive any dose of assigned study therapy or formally withdrew consent.

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

Primary Outcome Measure(s):
Progression-Free Survival (PFS): Defined as the time (in months) from treatment initiation to the first documented disease progression or death from any cause, whichever occurs first. This endpoint will be assessed using standard criteria (e.g., IMWG criteria) and analyzed via Kaplan--Meier survival curves and Cox proportional hazards models.
Secondary Outcome Measure(s):
Overall Survival (OS): Defined as the time from treatment initiation to death from any cause. OS will be analyzed similarly to PFS.
Response Rates: Including overall response rate (ORR) and the rate of complete response (CR) or better, as defined by the International Myeloma Working Group (IMWG) criteria. Response categories will include partial response (PR), very good partial response (VGPR), and complete response (CR).
Safety Outcomes: Evaluated by the incidence and severity of adverse events, specifically focusing on grade >=3 events such as infections, hematologic toxicities, and peripheral neuropathy. Adverse events will be categorized using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

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

The primary independent variable is the treatment regimen, categorized into four groups:

DVMP: Daratumumab + Bortezomib + Melphalan + Prednisone
VMP: Bortezomib + Melphalan + Prednisone
DRd: Daratumumab + Lenalidomide + Dexamethasone
Rd: Lenalidomide + Dexamethasone
Each category corresponds to the original study arm assignments in ALCYONE (DVMP vs. VMP) and MAIA (DRd vs. Rd).

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

In addition to the primary treatment variable, we will incorporate several covariates for both descriptive and analytic purposes:

Age (continuous, with possible categorization for subgroup analyses, e.g., 65--74 vs. >=75).
Sex (male/female).
Geographical Region (e.g., North America vs. other).
Race (White, Black, Asian, Other).
Baseline Creatinine Clearance (continuous, with potential categorization <60 vs. >=60 mL/min).
Type of Myeloma (IgG, IgA, other).
Hepatic Function (normal vs. impaired).
ECOG Performance Status (0--2, with higher scores indicating poorer function).

These covariates will be included in the propensity score model to minimize confounding and ensure well-balanced treatment comparisons.

Statistical Analysis Plan:

Descriptive Analyses: Summaries of baseline characteristics (means +/- SD or medians [ranges] for continuous variables; frequencies/percentages for categorical variables) will be provided for each treatment group, both before and after propensity score matching.

Propensity Score Estimation: A logistic regression model incorporating pre-specified covariates (age, sex, region, race, renal function, myeloma subtype, hepatic status, ECOG) will be used to generate propensity scores.

Matching: Nearest neighbor matching using a caliper of 0.2 SD of the logit of the propensity score.

We will evaluate balance by calculating standardized mean differences (<0.1 as the threshold for adequate balance).

Primary Analysis: SLP and SG: Kaplan--Meier and log-rank tests, hazard ratios from Cox models. Response and Safety: Logistic regression for binary endpoints (overall response, CR, grade >=3 adverse events).

Sensitivity Analyses: Alternate approaches (e.g., IPTW) and subgroups (e.g., older vs. very old, ECOG 0--1 vs. 2) to assess the consistency of findings.

Software Used:

R

Project Timeline:

Month 0: Secure YODA Project approval and data access; conduct preliminary review of ALCYONE and MAIA datasets.
Month 1: Data cleaning, harmonization, and identification of high-risk cytogenetic patients. Estimate propensity scores and assess baseline balance.
Month 2: Execute nearest neighbor matching, conduct primary analyses (PFS, OS), and perform logistic regression for safety/response. Undertake sensitivity analyses (IPTW).
Month 3: Finalize all analyses and compile a comprehensive report of findings. Prepare descriptive tables and figures.
Month 4: Share results with YODA and prepare a manuscript for submission to a peer-reviewed journal. Develop presentation materials for major conferences such as the International Myeloma Society Symposium.

Dissemination Plan:

We plan to disseminate results via: Peer-Reviewed Publication in a leading hematology/oncology journal (e.g., Blood, Leukemia, Haematologica).

Conference Presentations at international venues, including the International Myeloma Society Symposium and relevant Latin American hematology meetings.

Reporting to YODA, ensuring public access to detailed findings that may influence evidence-based clinical guidelines and future investigations.

Bibliography:

1. Fonseca R, Facon T, Hashim M, Nair S, He J, Ammann EM, et al. First-line use of daratumumab, lenalidomide, and dexamethasone confers survival benefit compared with second-line use of daratumumab-based regimens in transplant-ineligible patients with multiple myeloma: Analysis of different clinical scenarios. Blood. 2021;138(Suppl 1):118.

2. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022;97(8):1086-1107. doi:10.1002/ajh.26590. PMID:35560063; PMCID:PMC9387011.

3. Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10. PMID:

31836199.

4. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al; MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019 May 30;380(22):2104-2115. doi:10.1056/NEJMoa1817249. PMID:31141632; PMCID:PMC10045721.

5. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399-424.