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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/system/files/yoda_project_coi_form_sg.pdf
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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

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

Research Proposal

Project Title

Impact of frailty on outcomes of patients treated with Daratumumab, Lenalidomide and Dexamethasone for newly diagnosed Multiple Myeloma

Narrative Summary:

Older adults with MM are at an increased risk of treatment related toxicity, and inferior survival. In 2014, the international myeloma working group (IMWG) proposed a frailty index to identify transplant ineligible patients with newly diagnosed Multiple Myeloma at greatest risk of toxicities. Currently, it is unknown how frailty impacts outcomes of newly diagnosed transplant ineligible patients with MM (TiMM) treated with novel first line therapies. We propose to perform an exploratory analysis of the MAIA clinical trial to explore the role of frailty on outcomes of patients treated with Daratumumab, lenalidomide and dexamethasone among newly diagnosed TiMM.

Scientific Abstract:

Background: The addition of Daratumumab to lenalidomide and dexamethasone has been shown to improve response rate and progression free survival among newly diagnosed transplant ineligible older adults with Multiple Myeloma. The risk/benefit profile of this triplet thearpy among frail older adults remains unclear.
Objective: To explore the role of frailty on relative efficacy and toxicity outcomes among patients treated with Daratumumab, lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone among newly diagnosed transplant ineligible older adults with Multiple Myeloma.
Study Design: Exploratory post-hoc analysis of individual patient data from MAIA trial. Frailty will be constructed using baseline variables (age, ECOG performance status and comorbidities) as described by Facon et al.
Participants: Newly diagnosed Adult participants who participated in MAIA study who are ineligible for autologous stem cell transplantation due to age (?65y) or due to coexisting conditions.
Main Outcome Measure: The primary outcome of interest is progression free survival, defined as the time from randomization to progression or death, whichever occurs earlier. Secondary outcomes include response rate, overall survival and grade 3 or higher toxicities during therapy.
Statistical Analysis: Exploratory post-hoc analysis of individual patient

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Brief Project Background and Statement of Project Significance:

The introduction of monoclonal antibodies targeting surface molecules expressed on malignant plasma cells has significantly altered the treatment landscape of MM. Daratumumab, a human IgG1? monoclonal antibody that binds to CD38-expressing cells, induces tumor cell death through diverse immune-mediated actions, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell phagocytosis, as well as induction of apoptosis and modulation of CD38 enzymatic activities. After promising efficacy both as a single agent2 as well as in combination with established anti-myeloma regimens in the relapsed/refractory setting3,4, daratumumab was quickly incorporated in first-line trials, both in the transplant-eligible and transplant-ineligible setting. Recently, the MAIA trial tested Daratumumab added to Lenalidomide and Dexamethasone (Dara-RD) vs. RD alone among patients with NDMM not eligible for AHCT. Complete response rates (48% vs 25%) and PFS (HR 0.56; 95% 0.43-0.73) were significantly better in the Dara-RD arm.5

Because older patients are at an increased risk of treatment-related toxicity, there is a need to personalize treatment strategies based on their anticipated tolerance of treatment6. However, chronological age does not adequately capture this vulnerability due to the heterogeneity of patients in physical and psychological functioning. In 2014, the International Myeloma Working Group (IMWG) introduced a frailty score based on age, comorbidities and functional status and showed that frail patients (defined by a frailty score of 2 or higher) had a significantly inferior survival, greater treatment-related toxicity and discontinuation of therapy7. The German group proposed an alternative risk assessment tool, the Revised Myeloma Comorbidity Index (R-MCI), incorporating organ function (renal, lung), performance status, age and Fried frailty, and showed that the R-MCI outperformed other commonly used comorbidity indices to predict overall survival8.

More recently, Dr. Facon and colleagues proposed a simple, dichotomous, easy-to-use frailty score to predict clinical outcomes among transplant-ineligible older adults with multiple myeloma (MM)9. Using data from the FIRST trial, the authors classified patients into frail/non-frail based on age, comorbidities and Eastern Cooperative Oncology Group performance status (ECOG PS). Patients categorized as frail had significantly worse progression-free survival (PFS) and overall survival (OS), as well as higher rates of grade 3/4 treatment-related toxicities9.

Despite, increasing recognition of frailty and its impact on treatment related toxicities and survival among older adults with MM, clinical trials rarely include this information to select or stratify patients with MM, leading to a gap in literature regarding the incremental value of novel therapies and regimens for frail older MM patients. In this project, we propose to fill that gap by proposing an post-hoc exploratory analysis of the MAIA trial to study the incremental benefit of Daratumumab among older frail patients with MM.

Specific Aims of the Project:

a) To compare the clinical benefit of Daratumumab, Lenalidomide and Dexamethasone vs lenalidomide dexamethasone alone among frail and non-frail older adults with newly diagnosed Multiple Myeloma who are ineligible for autologous stem cell transplantation.

b) To compare the risk of cumulative grade 3 or higher toxicity of Daratumumab, Lenalidomide and Dexamethasone among older frail and non-frail older adults with newly diagnosed Multiple Myeloma who are ineligible for autologous stem cell transplantation.

We hypothesize that frail older adults with newly diagnosed transplant ineligible patients with Multiple Myeloma derive a similar benefit as non-frail older adults without a significantly increased risk of excess toxicity.

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
New research question to examine treatment safety

Research Methods

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

We will use the eligibility criteria from the MAIA study which includes the following:
Eligible patients had documented newly diagnosed multiple myeloma, with an Eastern Cooperative Oncology Group performance status score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability), and were ineligible for high-dose chemotherapy with stem cell transplantation owing to age (?65 years) or to the presence of coexisting conditions that were likely to result in the development of unacceptable side effects associated with high-dose chemotherapy with stem-cell transplantation.

Main Outcome Measure and how it will be categorized/defined for your study:

The primary endpoint includes the following:
a) Progression Free Survival: defined as time from randomization to progression or death.

Secondary Endpoints Include the following

b) Overall Survival: defined as time from randomization to death.
c) Overall Response Rate: defined using 2014 International Myeloma Working Group Response criteria10.
d) Grade ¾ Adverse Events (overall and itemized) in the safety population

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

e) Treatment Arm: Dara-RD vs RD arm

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

a) Frailty: defined according to Facon et al, using a composite score of age, ECOG performance status and charlson comorbidity score.
b) Sex
c) Race/Ethnicity
d) ISS stage
e) Presence/Absence of high risk cytogenetics
f) M protein Isotype:
g) Pretreatment absolute neutrophil and lymphocyte count.

Statistical Analysis Plan:

This is an exploratory post-hoc analysis of individual patient data from MAIA trial. Given that frailty was not a stratification factor used during randomization, we will account for all confounding variables in a multivariable analysis.
First, we will construct frailty categories (frail vs non-frail) as described by Facon et al, using a composite of age, ECOG performance status, and Charlson comorbidity index. We will use descriptive statistics and bivariate comparisons between the baseline characteristics between the frail and the non-frail subsets. We will test the impact of frailty on progression free and overall survival of the overall study cohort using Kaplan Meir Methods and compare the distributions using log-rank test. We will then study the impact of frailty on efficacy and toxicity outcomes using distribution appropriate multivariable models where we will test for statistical interaction between frailty category and treatment arm. This will comprise of Cox regression models for time to event data and logistic regression models for response rate (presence or absence of partial response/complete response etc). Similarly, best fit count models (poisson, zero inflated or negative binomial model) will be used to model cumulative toxicity events per patient during the treatment period. Each of these models will adjust for baseline covariates and will include frailty and treatment arm as well as the interaction term between the latter two. This will be followed by exploratory analysis within frail and non-frail subsets. Statistical analysis will be done using STATA and R softwares. All hypothesis testing will be two sided and the level of significance will chosen as 0.05.
Software Used:
STATA
Project Timeline:

YODA project approval/data availability: 4/2021

Data analysis to abstract preparation: 5/2021 to 8/2021
Abstract preparation to manuscript submission: 9/2021 to 12/2021

Dissemination Plan:

The results from the data analysis will be shared with YODA and thereafter abstract will be submitted to the Annual Society of Hematology meeting (ASH) 2021. The manuscript will then be simultaneously be prepared for submission by 11/2021 for consideration of publication in high impact medical journals such as Jama Oncology, Leukemia or Lancet Hematology.

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