

## Principal Investigator

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## General Information

**Key Personnel (in addition to PI):**

**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?:** Internet Search

## Conflict of Interest

[https://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2019\\_signed\\_0.pdf](https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_signed_0.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. [NCT02076009 - 54767414MMY3003 - Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone \(DRd\) vs Lenalidomide and Dexamethasone \(Rd\) in Subjects With Relapsed or Refractory Multiple Myeloma](#)
2. [NCT02136134 - 54767414MMY3004 - Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone \(DVd\) vs Bortezomib and Dexamethasone \(Vd\) in Subjects With Relapsed or Refractory Multiple Myeloma](#)
3. [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 Daratumumab on the Risk of Venous Thromboembolism in Patients with Multiple Myeloma: A Post-hoc Analysis of Phase III trials

### **Narrative Summary:**

Patients with multiple myeloma (MM) have an increased risk of venous thromboembolism (VTE), which is related to treatment regimen. Daratumumab has been increasingly used in patients with newly diagnosed or relapsed/refractory MM. However, its association with VTE is largely unknown. In this study, we aim to compare the risks of VTE between daratumumab-containing and non-daratumumab regimen in randomized controlled trials (RCTs) using individual participant data (IPD). The results of the study will help clinicians better understand the risk of VTE in patients of MM and guide proper VTE prophylaxis in these patients.

### **Scientific Abstract:**

**Background:** Patients with multiple myeloma (MM) have an increased risk of venous thromboembolism (VTE), and the risk is modified by treatment regimen. It is unknown if daratumumab can affect VTE risk.

**Objective:** To evaluate the association between daratumumab use and the development of VTE.

**Study design:** Using IPD from YODA, we will perform time-to-event analysis of VTE in patients receiving daratumumab-containing (dara) regimen and non-daratumumab (non-dara) regimen, and validate traditional risk scores for VTE in patients with MM.

**Participants:** Patients in phase III RCTs which compare the efficacy of dara and non-dara regimens.

**Main outcome measures:** Risk of VTE in patients receiving dara and non-dara regimen.

**Statistical analysis:** Fine-Gray competing risk regression model to evaluate the association between daratumumab use and development of VTE. Analyses will be stratified by the type of chemotherapy regimen used and adjusted for VTE risk factors. Next, for patients receiving dara regimen, we will validate the VTE risk score in MM proposed by the International Myeloma Working Group (IMWG) using Kaplan-Meier method.

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

The association between cancer and VTE has been well documented. For patients with MM, the risk of VTE is modified by disease status, patient factors, as well as treatment regimen. (1) Indeed, for those who received immunomodulatory drugs (IMiD) such as thalidomide and lenalidomide in conjugation with other agents, the incidence of VTE can be as high as 20% if no prophylaxis was given. (2) Daratumumab, an anti-CD38 monoclonal antibody, has shown superior clinical efficacy as a new class of medication. (3,4) It has been approved by FDA in both treatment naïve and relapsed/refractory MM. However, its association with VTE has not been studied as per our knowledge. Given CD38 playing a critical role in procoagulant activity of platelets and hemostasis (5), we postulate daratumumab could be associated with a lower risk of VTE in patients with MM.

The results of the study will help clinicians better stratify the risk of VTE in patients with MM. It will also provide insights as what type of VTE prophylaxis will be needed for patients receiving daratumumab.

### **Specific Aims of the Project:**

**Specific Aim 1:** To compare the risk of VTE between dara and non-dara regimen, in post-hoc analysis of phase III RCTs, after adjusting for baseline risk factors for VTE.

**Hypothesis:** Dara regimen will be associated with a significantly lower risk of VTE comparing with non-dara regimen.

**Specific Aim 2:** To validate the IMWG's VTE risk stratification system in patients receiving daratumumab.

**Hypothesis:** Patients on daratumumab with different IMWG VTE score will have significant difference of VTE risk.

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

New research question to examine treatment safety

Research on comparison group

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:

Data Source: IPD of the following trials:

NCT02076009: DRd vs Rd in relapsed/refractory MM

NCT02136134: DVd vs Vd in relapsed/refractory MM

NCT02252172: DRd vs Rd in previously untreated MM

Inclusion Criteria:

Adult patients with VTE occurring after starting treatment, with or without VTE prophylaxis

Exclusion Criteria:

Patients cross over to the other treatment group

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

Main outcome measure will be VTE events occurring anytime during trial period. VTE event is a composite endpoint of deep vein thrombosis and pulmonary embolism including catheter-associated VTE.

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

For Specific Aim 1: the main predictor is the use of daratumumab

For Specific Aim 2: the main predictor is the IMWG's VTE risk score, which includes obesity (BMI $\geq$ 30), previous VTE, central venous catheter/pacemaker, associated disease (including cardiac disease, chronic kidney disease, diabetes, acute infection, and immobilization), surgery/trauma and use of erythropoietin. Patients with 0 or 1 risk factor is considered low risk; patients with 2 or more risk factors are considered high risk.

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

- 1) Confounding variables for Specific Aim 1 including traditional VTE risk factors: age, sex, BMI, smoking status, performance status, recent surgery, and previous VTE
- 2) Death will be a competing risk factor for VTE occurrence, for both Specific Aim 1 and 2.
- 3) Thrombocytopenia is a common adverse effect of daratumumab. The incidence of thrombocytopenia will be compared between dara and non-dara groups.
- 4) Biochemical measure of disease severity: M-protein level at the time of chemotherapy initiation

## Statistical Analysis Plan:

1) Aim 1: first we will compare baseline characteristics of patients in the dara and non-dara group, as well as incidence of VTE incidence in the two groups. We will use descriptive statistical methods, and characteristics we will compare include age, sex, BMI, smoking status, performance status, recent surgery, previous VTE, M-protein level, and incidence of thrombocytopenia during treatment. Then we will perform Fine-Gray competing risk regression model (6) of VTE occurrence, adjusting for VTE risk factors (age, sex, BMI, smoking status, performance status, recent surgery, and previous VTE).

2) Aim 2: first we will determine the risk of VTE for each patient receiving daratumumab according to the IMWG's risk stratification. Patient then will be divided into low-risk and high-risk group. Kaplan-Meier method will be used to compare the incidence of VTE between low-risk and high-risk group.

Software Used:

RStudio

## Project Timeline:

Once study is approved and data access provided (assuming by August 2020), our key milestones dates are:

Project start: August 1, 2020

Data collection and analysis completion: September 1, 2020

Manuscript drafted and submitted for publication: October 1, 2020

Date results reported back to YODA: October 1, 2020

## Dissemination Plan:

We anticipate generating one manuscript from the project. We aim to submit the manuscript to the oncology/hematology journals, such as Blood Cancer Journal. The target audience will be primary care physicians, hematologists/oncologists as well as physician-scientists with interest in coagulation pathway.

### **Bibliography:**

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6. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496-509