

**The YODA Project
Research Proposal Review**

The following page contains the final YODA Project review
approving this proposal.

The YODA Project
Research Proposal Review - Final
(Protocol #: 2022-5048)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross
- Joshua Wallach

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | Yes |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Approve |

Comments:

No additional comments

**The YODA Project
Research Proposal Review**

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and
the original submitted proposal.

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2022-5048)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross
- Joshua Wallach

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | No |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Not Approve |

Comments:

1. Please clarify whether this is a network meta-analysis, which seeks to compare the efficacy of different MM treatments in both a direct and indirect manner, or whether the sole focus of the analysis will be on daratumumab vs placebo. If you are conducting a NMA, that should be specified and included in the methods.
2. The protocol also states that identifying predictors of adverse outcome is a priority; further clarification of how the patient characteristics will be evaluated on the context of different treatments received will be helpful. That is, are you exploring risk factors for toxicity after daratumumab receipt, or alternatively across all treatment groups, and adjusting for treatment?

Principal Investigator

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Key Personnel (in addition to PI):

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Last name: Hopkins
Degree: PhD
Primary Affiliation: Flinders University
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First Name: Michael
Last name: Sorich
Degree: PhD
Primary Affiliation: Flinders University
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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?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_2022_ahmad_abuhelwa_signed.pdf

https://yoda.yale.edu/system/files/ashley_hopkins_coi.pdf

https://yoda.yale.edu/system/files/michael_sorich_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. [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. [NCT00574288 - 54767414GEN501 - Daratumumab \(HuMax®-CD38\) Safety Study in Multiple Myeloma - Open Label, Dose-escalation Followed by Open Label, Single-arm Study](#)
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. [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

Predictors of exposure, therapeutic and adverse effects of medicines used in the treatment of multiple myeloma

Narrative Summary:

Multiple myeloma (MM) is a cancer of plasma cells and is on the rise worldwide. Since 1990, the MM incidence has increased by 126% globally and by 40% in the US, whilst global mortality has increased by 94% [1].

There are many important medicines used in MM treatment including daratumumab. However, response and toxicity to daratumumab is highly variable and there are no accurate and reliable tools to date to accurately predict patients who will benefit most. Using the diverse range of data from MM clinical trials, it is possible to identify predictors and develop clinical tools that enable improved prediction of daratumumab treatment outcomes and inform better treatment decisions.

Scientific Abstract:

Background: Multiple myeloma (MM) is a cancer of plasma cells and is on the rise worldwide, particularly in the US, Australia, and Western Europe. Nearly 2% of cancer diagnoses and more than 2% of cancer deaths in the US are due to MM. Since 1990, the global incidence of MM has increased by 126% and US incidence by over 40%, whilst global mortality has increased by 94%. Daratumumab is an important treatment option for patients with MM. However, response and toxicity to daratumumab can be highly unpredictable.

Objectives: To identify predictors and develop predictive models of therapeutic and adverse effect outcomes of daratumumab used to treat MM. Being able to identify the expected response and adverse effect profile may enable patients and clinicians to make better decisions regarding whether to commence, continue or change dosing of daratumumab for the treatment of MM.

Study design: A pooled observational cohort analysis of available clinical trial individual-participant data.

Participants: MM patients treated with daratumumab or relevant comparator arms

Main Outcome Measure(s): response (early, depth, best overall), overall survival, progression-free survival, adverse event outcomes (clinician/patient reported adverse effects that have been defined according to the international common toxicity criteria, and adverse events requiring medication changes).

Statistical analysis: Cox-proportional hazard/time-to-event models will be used to assess the association between potential predictors and the time to an adverse effect or survival time. The association of potential predictors with

binary outcomes (e.g., best overall response) will be modelled using logistic regression and will be reported as odds ratios with 95% confidence intervals. Longitudinal analysis (e.g., linear, and non-linear mixed effect modelling) will be used to assess the nature and patterns of longitudinal changes of key continuous variables (e.g., drug concentration, neutrophil counts).

Crude associations will be reported based on univariate analysis (adjusting only for the study population and treatment arm), and adjusted associations based on a multivariable analysis. Continuous variables will be assessed for non-linearity of association with outcomes using restricted cubic splines. Should multiple values of an assessed covariate be recorded for a single visit (e.g. blood pressure) the mean of the multiple reads will be used. The varying performance of clinical prediction models developed using multivariable analysis techniques including stepwise regressions, penalised methods [which minimise the risk of overfitting (e.g., elastic net analysis)], and machine learning [which excel in optimising prediction with high-dimensional data (e.g., random forest and gradient boosted methods)] will be assessed. Early markers of exposure, response and toxicity will be evaluated using a landmark approach where possible, with sensitivity analyses based on the use of time-dependent covariates. Landmark time will be dependent on the time points available in individual studies, and the time frame of changes in each specific predictor variable.

Analyses will include evaluating the heterogeneity in outcome predictors for MM drugs as compared to relevant comparator. Such evaluations will allow a better understanding of whether the relationships identified are specific to a specific MM drug or are common to standard treatment (i.e., common prognostic factors).

Brief Project Background and Statement of Project Significance:

There are many important medicines used in the treatment of MM including daratumumab. However, response and toxicity to daratumumab is highly unpredictable. For example, ~35 of the patients who initiate daratumumab therapy for MM do not respond to therapy and experience serious toxicity. Thus, more research is required to confirm and explore novel predictive markers of therapeutic and adverse effects of daratumumab used in the treatment of MM.

This project seeks to enable improved prediction of the therapeutic and adverse outcomes of patients using medicines for the treatment of MM. This project with daratumumab data is part of a bigger project submitted to Vivli (Vivli Project ID: 00008427) where available data from other MM drugs (ixazomib, isatuximab) will be meta-analysed to identify the most important predictors of response for medicines used in the treatment of patients with MM.

Ultimately developing clinical prediction models for medicines used to treat MM will enable patients and clinicians to make informed shared treatment decisions as to whether to commence, continue, discontinue or change dosing of these medicines which can eventually lead to improved health outcomes and significant cost savings.

Specific Aims of the Project:

The hypothesis of this project is that clinical predictors of response and adverse effects to daratumumab can be developed from clinical trial data to enable informed decisions by patients and clinicians.

Specific aims:

1. Identify baseline and on-treatment predictors and develop clinical prediction models of the key therapeutic outcomes (response, progression and survival) of medicines used in the treatment of MM.
2. Identify baseline and on-treatment predictors and develop clinical prediction models of the key adverse effects of medicines used in the treatment of MM.
3. Evaluate the heterogeneity of treatment and adverse effect predictors for MM drugs versus comparator therapies.

These analyses are primarily hypothesis generating and they will require subsequent validation.

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

Meta-analysis using data from the YODA Project and other data sources

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

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:

To precisely and validly determine the relationship between potential predictors and outcomes of interest it is important to have the maximum sample size possible across a range of different study populations (an increased number of studies increases the population diversity, and is thus more comparable to standard clinical practice). Therefore, all studies collecting baseline and follow-up clinical characteristic data, as well as adverse event or therapeutic outcome data for cancer patients treated with daratumumab have been selected (model building will use the per-protocol populations). Data from the comparator arms will be required to understand the heterogeneity in predictors between primary and comparator treatments (analyses of the heterogeneity of treatment effects will use the intent-to-treat populations).

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

Data for main outcome measures include response (early, depth, best overall), overall survival, progression-free survival, adverse event outcomes (clinician/patient reported adverse effects that have been defined according to the international common toxicity criteria, and adverse events requiring medication changes), and drug exposure (concentration). The most recent in scope data cuts of these variables are required.

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

It is important to have access to all the baseline and follow-up clinical/biological/patient characteristic data collected on an individual for any given study. Covariates to be explored include, but not limited to:

- Baseline values. defined as the value closest and prior to the first dose of study treatment. Variables include:
- Basic patient characteristics – e.g. age, sex, race/ethnicity, body mass index (BMI), weight, weight loss prior to diagnosis and therapy initiation, smoking status, alcohol consumption, family history of disorders, and measures of performance status
- Laboratory data - e.g. levels of lactate dehydrogenase, alkaline phosphatase, albumin, bilirubin, leucocyte and leucocyte subtype counts (e.g. total white blood cells (WBC), lymphocyte, monocyte or eosinophils, neutrophil to lymphocyte ration (NLR), lymphocyte to monocyte ratio (LMR), platelets to lymphocyte ration (PLR)), haemoglobin, platelets, glucose, hemoglobin A1c (HBA1C), creatinine, C-reactive protein, circulating tumour cells, calcium, total protein, total triglycerides, cholesterol, blood urea nitrogen, international normalized ratio, and anaemia.

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

- Disease classification data - e.g. tumour stage and grade, site and histology/subtype of primary tumour, prior therapy, prior surgery, time to response / progression for previous therapies, time since diagnosis, number and sites of metastases, mutation and expression status of disease specific oncogenes, line of therapy, pathological features of tumour cells, tumour infiltrating lymphocytes, number of nodes with tumour, cancer antigen level.
- Patient-reported outcomes: patient-reported physical function, fatigue, global health, emotional function.
- Other common predictors – e.g. concomitant medications, respiratory comorbidity (e.g. asthma / chronic obstructive pulmonary disease (COPD)), other comorbid diseases (e.g. peripheral vascular disease, cerebrovascular disease, diabetes, Hepatitis C infection), simplified comorbidity score, organ dysfunction (e.g. liver, lung or renal impairment), and other clinical, biological, vital statistics, laboratory, imaging, pharmacokinetic and patient-reported outcomes measures.

Most recent data cuts of these variables are required.

Statistical Analysis Plan:

The analysis for this project will be completed on Vivli platform. Other studies requested from vivli include: NCT01564537, NCT02312258, NCT02046070, NCT01850524, and NCT02990338.

Cox-proportional hazard/time-to-event models will be used to assess the association between potential predictors and the time to an adverse effect or survival time. Associations will be reported primarily as hazard ratios with 95% confidence intervals. The association of potential predictors with binary outcomes (e.g., best overall response) will be modelled using logistic regression and will be reported as odds ratios with 95% confidence intervals. Longitudinal analysis (e.g., linear, and non-linear mixed effect modelling) will be used to assess the nature and patterns of longitudinal changes of key continuous variables (e.g., drug concentration, neutrophil counts).

Crude associations will be reported based on univariate analysis (adjusting only for the study population and treatment arm), and adjusted associations based on a multivariable analysis. Continuous variables will be assessed for non-linearity of association with outcomes using restricted cubic splines. Should multiple values of an assessed covariate be recorded for a single visit (e.g. blood pressure) the mean of the multiple reads will be used. The varying performance of clinical prediction models developed using multivariable analysis techniques including stepwise regressions, penalised methods [which minimise the risk of overfitting (e.g., elastic net analysis)], and machine learning [which excel in optimising prediction with high-dimensional data (e.g., random forest and gradient boosted methods)] will be assessed. Early markers of exposure, response and toxicity will be evaluated using a landmark approach where possible, with sensitivity analyses based on the use of time-dependent covariates. Landmark time will be dependent on the time points available in individual studies, and the time frame of changes in each specific predictor variable. As our analyses are primarily hypothesis generating and they will require subsequent validation, no formal adjustment for multiple testing is intended. However, this limitation will be clearly stated in any publications of results. As it is expected that < 5% of data will be missing for assessed variables, complete case analyses are planned. Should variables with substantial missing data be present, the pattern and likely cause of the missing data will be evaluated and if missing at random is reasonable to assume then single regression imputation will be undertaken.

Analyses will include evaluating the heterogeneity in outcome predictors for MM drugs as compared to relevant comparator. Such evaluations will allow a better understanding of whether the relationships identified are specific to a specific MM drug or are common to standard treatment (i.e., common prognostic factors).

Predictors that have a clinically meaningful (e.g., double the risk) effect on mortality and adverse effects will be of primary interest. Based upon a 30% incidence of toxicity, a sample size of approximately 600 is required to detect a predictor (with a 10% frequency within the population) associated with a two-fold risk ($\alpha=0.05$ with 80% power). Based upon an event rate of 40% during trial follow-up (e.g., for progression), approximately 450 participants are required for 80% power to detect a predictor (with a 10% frequency within the population) associated with a two-fold hazard of the event ($\alpha=0.05$). These sample sizes are well within scope for this study.

Data will be explored for inconsistencies in time recordings, physiologically unreasonable covariate values, and unit errors. Prior to beginning analyses, individual data values will be extracted/constructed based on the raw and analysis datasets provided and will be checked against pertinent results in published manuscripts or clinical study reports (CSRs) relating to the specific trial.

Software Used:

RStudio

Project Timeline:

The project is expected to take 1 year from the date of data access. Estimated start date 1 January 2023 with all analysis completed by 1 January 2023. Manuscripts will be drafted and submitted at each stage of the proposed project. Results will be reported back to YODA following manuscript revisions and acceptance.

Dissemination Plan:

Results of all completed analyses will be published in peer-reviewed international publications and where possible also presented at scientific meetings. Manuscript(s) will be targeted primarily to international oncology journals (e.g. European Journal of Cancer, International Journal of Cancer, Cancers) and will be submitted as soon as possible

following completion of the requisite analyses.

Bibliography:

[1] Padala SA, Barsouk A, Barsouk A, Rawla P, Vakiti A, Kolhe R, et al. Epidemiology, Staging, and Management of Multiple Myeloma. *Med Sci (Basel)*. 2021;9(1).