Principal Investigator

First Name: Ahmad
Last Name: Abuhelwa
Degree: Doctor of Philosophy
Primary Affiliation: University of Sharjah
E-mail: ahmad.abuhelwa@sharjah.ac.ae
Phone number: +971501141990
Address: University of Sharjah, United Arab Emirates

City: Sharjah
State or Province: Sharjah
Zip or Postal Code: 00000
Country: United Arab Emirates
SCOPUS ID: 56588047800

General Information

Key Personnel (in addition to PI):

First Name: Ashley
Last name: Hopkins
Degree: PhD
Primary Affiliation: Flinders University
SCOPUS ID: 0000-0001-7652-4378

First Name: Michael
Last name: Sorich
Degree: PhD
Primary Affiliation: Flinders University
SCOPUS ID: 0000-0003-1999-866X

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 >2% of cancer deaths in the US are due to MM. Since 1990, global incidence of MM has increased by 126% and US incidence by >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 medicines 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 medicines used to treat MM.

Study design: An observational cohort analysis of clinical trials 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), and drug exposure (concentration).

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, about 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 used to identify the most important predictors of treatment outcomes in 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 of MM drugs 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 your Study Design?:

Meta-analysis (analysis of multiple trials together)

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

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

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

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:

Access to the individual baseline and follow-up clinical/biological/patient characteristic data for a given study is important. Predictors to be explored include, but not limited to:

• Basic patient characteristics: e.g. age, sex, race, body mass index (BMI), weight, weight loss, smoking status, alcohol consumption, and measures of performance status

• Laboratory data - e.g. levels of lactate dehydrogenase, alkaline phosphatase, albumin, bilirubin, leucocyte and leucocyte subtype counts, haemoglobin, platelets, C-reactive protein.

• Patient-reported outcomes: e.g. patient-reported physical function, fatigue, global health, emotional function.

• Concomitant medications: e.g. antibiotics, acid antisecretory drugs (e.g. proton pump inhibitors), antihypertensive drugs (betablocker, ACEI, CCB).

• Comorbidity data: family history of disorders (e.g. vascular disorders)

• Exposure data: number of completed cycles, drug concentrations

• Disease classification data - e.g. tumour grade, site and histology of primary tumour, prior therapy, time since diagnosis, number and sites of metastases, mutation and expression status of disease-specific oncogenes, line of therapy.

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

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• Laboratory data – including 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)), glucose, hemoglobin A1c (HBA1C), circulating tumour cells, calcium, total protein, total triglycerides, cholesterol, blood urea nitrogen, international normalized ratio, and anaemia.

• Other common predictors – e.g. 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 time to an adverse effect or survival. Associations will be reported as hazard ratios with 95% confidence intervals (CI). 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% CI. 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, 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). Where comparisons between treatments are made we will maintain the validity of randomized design as is typical to traditional subgroup analyses of RCT data.

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 (?=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 (?=0.05). These samples sizes are well within scope of 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 constructed based on the raw and analysis datasets and will be checked against published manuscripts or CSRs.
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 2024. 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:

Through this project we will publish works identifying baseline and on-treatment predictors and develop clinical prediction models of the key therapeutic and adverse outcomes of medicines used in the treatment of MM. Predictors will be explored based on biological and clinical plausibility and prior research – notably including, patient characteristics, laboratory, disease classification, patient-reported outcome, concomitant medications, comorbidity, and exposure data. These domains will be explored as to whether they identify therapeutic and adverse outcomes for all patients with MM or are specific to individual treatments. Samples sizes are well within scope to investigate and publish information across these degrees of freedom. It is anticipated, but will be informed by analyses, that several publications may arise from this project, including for the pooled population or for predictors identified as specific to individual treatments. Manuscripts 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).

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