Principal Investigator

First Name: Diana
Last Name: Bayani
Degree: MSc
Primary Affiliation: National University of Singapore
E-mail: dbayani@u.nus.edu
Phone number: +6587896288
Address: Singapore
City: Singapore
State or Province: Singapore
Zip or Postal Code: 117549
Country: Singapore

General Information

Key Personnel (in addition to PI):
First Name: Diana Beatriz
Last name: Bayani
Degree: BA, MSc
Primary Affiliation: National University of Singapore

First Name: Hwee-Lin
Last name: Wee
Degree: PhD
Primary Affiliation: National University of Singapore

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?: Scientific Publication

Conflict of Interest


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

Indirect comparison of daratumumab-based regimen versus bortezomib, lenalidomide, and dexamethasone for newly diagnosed, transplant ineligible MM

Narrative Summary:

Benefits of multiple myeloma (MM) drugs are measured in clinical trials, which are considered the gold standard. However, some studies are limited because these are compared against a specific therapy and may not be generalizable. When new drugs are assessed for value-for-money, it is important to have data relevant to local health practice. In the absence of clinical studies that compare the relevant treatments against each other, statistical techniques can be applied to existing data to estimate the outcomes that are more clinically relevant in local context. This research aims to estimate benefits of using daratumumab among NDMM patients using individual patient data from trials.

Scientific Abstract:

Background: There is no existing study directly comparing daratumumab-based regimens with the current standard regimen of bortezomib, lenalidomide, and dexamethasone for untreated patients ineligible for transplant. A proper comparison of the two regimens is necessary especially when conducting an economic evaluation relevant to local context.

Objective This study aims to conduct an indirect comparison between daratumumab, lenalidomide, and dexamethasone (DRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for newly diagnosed multiple myeloma patients who are transplant ineligible.

Study Design: A matching-adjusted indirect comparison (network meta-analysis) will be done to appropriately estimate the effect of the two regimens against a common comparator.

Participants: Trial participants from the MAIA trial will be the main data source, as well as a subgroup of patients who participated in the SWOG S0777 who are over 65 or did not get a transplant. Individual level data is needed from the MAIA trial, while only published data will be obtained from SWOG 0777.

Main Outcome Measure(s): The main outcome measure of interest is progression-free survival defined as time from randomization to disease progression or death.

Statistical Analysis: The MAIC method, which is a form of non-parametric likelihood reweighting using propensity scores, will be used. Relevant covariates’ outcome measures will be log-transformed to approximate normality ensure stability of the variance. After which, a logistic propensity score model will be developed which includes all relevant variables. Corresponding weights will be estimated using the method of moments to match the distribution of the variables between the two trials being compared. Outcomes of patients on daratumumab from the MAIA trial can then be predicted using the reweighted, matching-adjusted data from the comparator trial (SWOG S0777).

Brief Project Background and Statement of Project Significance:

Daratumumab, an anti-CD38 monoclonal antibody, has shown to be effective in the treatment of relapsed or refractory multiple myeloma, when used in combination with two other drugs, as demonstrated in the POLLUX, CASTOR, and CANDOR trials. In contrast, while its use in the newly diagnosed population is less common, there is strong interest after seeing positive results from the MAIA and ALCYONE studies for the transplant ineligible population.

In Singapore context, the most common regimen used for transplant ineligible patients is bortezomib, lenalidomide, dexamethasone (VRd), based on results from SWOG S0777. There currently strong interest in using daratumumab as a potential upfront treatment, as a replacement to bortezomib (DRd). However, no head-to-head trials exist comparing a bortezomib based regimen with daratumumab, in combination with lenalidomide and dexamethasone. Further, no other meta-analysis for this specific research question has been conducted as of writing this proposal.

Comparative efficacy data is useful not only for clinician’s individual decision making for patients, but also for informing financing policies of payers. In most developed health systems, access to high-cost drugs are dependent on subsidy and coverage policies typically informed by health technology assessment (HTA) processes. As part of
HTA processes, the drugs are assessed against the relevant comparator, one that is used in current practice, to evaluate its cost-effectiveness. Given that the cost of most therapies for multiple myeloma are prohibitive, obtaining coverage or subsidy is essential to enable better access among patients.

One way to obtain clinically relevant efficacy data in the absence of head-to-head trials is by conducting an indirect comparison or network meta-analysis. This method relies on pooling of effects and anchoring on a common comparator used in the clinical trials. When there is significant heterogeneity between the two trials, more novel methods such as matching adjusted indirect comparison (MAICs) can be applied to address this and reduce uncertainty in the results. However, the feasibility of using such method is dependent on the availability of patient-level data from the selected trials.

The use of network meta-analyses and indirect comparisons are common and well-accepted by HTA agencies as a source of clinical effectiveness data for modelling studies. The absence of clinically relevant comparative effectiveness data may undermine the results of cost-effectiveness studies, especially when these are estimated against comparators not used in local context, e.g. using MAIA data alone. In Singapore’s HTA process, it is imperative to use appropriate sources to obtain both clinical outcomes and cost data in support of evidence submission for drug listing and subsidy.

Specific Aims of the Project:

The specific aim of the project is to conduct a matching-adjusted indirect comparison between daratumumab, lenalidomide, and dexamethasone (DRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for newly diagnosed, transplant ineligible multiple myeloma patients. This requires individual-level patient data to be feasible. The results of this study will be used as clinical outcomes input data for a planned evaluation that will assess the health and economic effects of first-line use of daratumumab compared to the current standard of care. The economic evaluation may be used to inform subsidy policy of daratumumab in Singapore.

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
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
Develop or refine statistical methods

Research Methods

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

The main data source will be all participants of the MAIA trial (n=737). Based on the trial’s inclusion and exclusion criteria, these are eligible patients with documented newly diagnosed multiple myeloma and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2. All these patients were ineligible for high-dose chemotherapy with stem-cell transplantation because of their age (65 years or older) or have comorbidities that will likely lead to side-effects from the high-dose chemotherapy or of the stem-cell transplant. Other criteria based on biomarkers were likewise applied.

The inclusion criteria for including SWOG S0777 trial patients will be more specific compared to the original criteria used in the trial. Because we are interested in transplant ineligible, newly diagnosed multiple myeloma patients, we will restrict patients to those who 65 years or older only, or those without an intent for immediate stem-cell transplant (n=315).

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

The main outcome measure of interest is progression-free survival defined as time from randomization to disease progression or death. The definition of progression is based on the criteria specified by the International Myeloma Working Group, which is a 25 percent increase from lowest response value in serum M protein, urine M protein, difference in the kappa and lambda FLC, or bone marrow plasma cell percentage.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The proposed matching-adjusted indirect comparison (MAIC) method requires a selection of certain covariates for calculating the propensity score, which will be used to predict the membership of patients between the two trials (i.e. index versus comparator). The factors to be considered in the propensity score estimation include patient’s age, gender, time since diagnosis, ECOG performance status, International Stage System based on serum albumin, myeloma subtype, serum beta-2 microglobulin and c-reactive protein concentration. When data is incomplete or unavailable, the variable will be excluded from the calculation of propensity score.

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

Aside from progression-free survival, we are also interested in comparing adverse event rates (safety) and rates of discontinuation between the two regimens. Both outcomes will be relevant especially when comparing costs associated with each regimen. Adverse events are graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, and include hematologic and nonhematologic events. In addition, it is of interest to know if any of these events have led to the discontinuation of treatment.

Statistical Analysis Plan:

The indirect comparison requires matching of trial populations and adjusting for the differences between the groups through the MAIC method, which is a form of non-parametric likelihood reweighting using propensity scores. This procedure is done after identifying the trials and specifying the outcome measure to be estimated.

MAIC is a novel method where traditional propensity scores and regression methods are applied specifically for the context of conducting an indirect comparisons with limited individual patient data (IPD). This addresses the issue common among indirect comparisons for health technology assessments where IPD may only be accessible for one study, and investigators are limited to accessing aggregate data for the other. MAIC uses inverse propensity score weighting to form weighted mean estimators of the expected mean outcomes on treatments and in the population, where the propensity scores are found using a method of moments as described by Signorovitch et al.

An anchored comparison will be done given that there is a common comparator between the MAIA and SWOG S0077 trial being lenalidomide and dexamethasone (Rd). These two trials were selected on the basis that they provide best evidence on the treatment effect of daratumumab and bortezomib based regimens, when compared to lenalidomide and dexamethasone alone.

To conduct the matching procedure, relevant covariates were selected based on existing data on predictors of disease progression for multiple myeloma. The measures will be log-transformed to approximate normality ensure stability of the variance. After which, a logistic propensity score model will be developed which includes all relevant variables. Corresponding weights will be estimated using the method of moments to match the distribution of the variables between the two trials being compared. Given that only aggregate data is available from SWOG 0777, only marginal covariate information (e.g. mean and standard deviation for continuous variables, proportions for categorical variables) and their corresponding distributions will be used. This assumes that either the joint distribution of covariates in the SWOG0777 trial is the product of the published marginal distributions or the correlations between covariates are the same as those observed in MAIA. Using a methods of moments estimator will allow for the weights to exactly balance the mean covariate values between the weighted MAIA population and the SWOG 0777 population. Outcomes of patients on daratumumab can then be predicted using the reweighted, matching-adjusted data from the comparator trial (SWOG S0777). The anchored indirect comparison can now be formed and the distribution of estimated weights and effective sample size can be presented. For detailed equations of the propensity score model, weight estimation using methods of moments, prediction of outcomes by reweighting, and indirect comparison, kindly refer to the NICE DSU Technical Support Document 18.

Individual patient-level data will only be obtained from the MAIA trial. Results from SWOG S0777 (NCT00644228) will be solely based on the published results from Durie, et al 2017, and a longer-term follow-up study published in 2020 in Blood Cancer Journal.

Software Used:
RStudio

Project Timeline:

The project will take around 9 months to complete, starting from the time that the individual patient-level data is
provided. Data cleaning and analysis will take up the bulk of the time, lasting for 3-4 months. After which, results will be synthesized and presented to internal stakeholders (research team and clinicians within the university) for peer review, prior to any external dissemination. We expect to have a manuscript drafted by the 6th month and submitted for publication before the 9th month. Results will be subsequently reported back to the YODA project before the end of the project’s timeline.

Dissemination Plan:

The desired output for this study is a publication in an international or local clinical journal such as Critical Reviews in Oncology/Hematology, Annals Academy of Medicine (Singapore), or HTA-focused journals such as Value in Health and PharmacoEconomics. It may be presented in internal meetings, research rounds, and in international fora.

Bibliography: