

Principal Investigator

First Name: Mark

Last Name: Yan

Degree: PhD

Primary Affiliation: Hoffmann-La Roche Limited

E-mail:

State or Province: CA

Country: USA

General Information

Key Personnel (other than PI):

First Name: Pascal

Last name: Chanu

Degree: PharmD

Primary Affiliation: Genetech/Roche

SCOPUS ID:

Requires Data Access? Unknown

First Name: Frederico

Last name: Mattiello

Degree: PhD

Primary Affiliation: F. Hoffmann-La Roche AG

SCOPUS ID:

Requires Data Access? Unknown

First Name: Mathilde

Last name: Marchand

Degree: PhD

Primary Affiliation: Certara

SCOPUS ID:

Requires Data Access? Unknown

How did you learn about the YODA Project?: Colleague

Conflict of Interest

[https://yoda.yale.edu/wp-](https://yoda.yale.edu/wp-content/uploads/2018/12/yoda_project_coi_form_for_data_requestors_2019_2021-4660_signed.pdf)

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<https://yoda.yale.edu/wp-content/uploads/2021/04/COI-FORM-MM.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](#)
4. [NCT03180736 - 54767414MMY3013 - A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor](#)
5. [NCT02195479 - 54767414MMY3007 - A Phase 3, Randomized, Controlled, Open-label Study of VELCADE \(Bortezomib\) Melphalan-Prednisone \(VMP\) Compared to Daratumumab in Combination With VMP \(D-VMP\), in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High-dose Therapy](#)

Research Proposal

Project Title

Associations between response, progression, and overall survival in phase III daratumumab clinical trials in relapsed/refractory multiple myeloma

Narrative Summary:

Improved response and survival in multiple myeloma (MM) patients have been steadily increasing over the past 5-10 years with the recent introduction of targeted therapies. Daratumumab has been available for the treatment of relapsed/refractory (RR)MM patients since 2015 leading to significant survival benefit. However, the link between response and clinical outcomes is unclear. In this proposed study, relationships between response, progression, and survival in RRMM will be assessed using individual patient-level clinical trial data. Results from this study will be used to inform and support decisions on clinical trial design and selection of optimal study endpoints for RRMM patients.

Scientific Abstract:

Background: The rapidly evolving treatment landscape of multiple myeloma (MM), especially the introduction of targeted therapies over the past few years has had a significant impact on clinical outcomes. In this proposed study, relationships between response, progression-free survival (PFS), and overall survival (OS) in relapsed/refractory (RR)MM patients will be evaluated using individual patient-level clinical trial data.

Objective: To assess relationships between response, PFS, and OS in RRMM patients

Study Design and Participants: Subjects diagnosed with RRMM who participated in the Phase 3 randomized studies for daratumumab: NCT02076009, NCT02136134

Main Outcome Measures: PFS and OS

Statistical Analysis: This is a post-hoc analysis of NCT02076009 and NCT02136134 evaluating associations between 1) response and OS, 2) response and PFS, and 3) PFS and OS using individual patient-level data. Subjects' response status based on the International Myeloma Working Group (IMWG) response criteria will be assessed as a predictor for PFS and OS using a multivariate Cox regression analysis with response as a time-varying covariate. Landmark analyses will also be conducted to evaluate the response-progression and response-survival relationships with response

categorized at fixed time points after treatment initiation (Anderson JR et al 2008; Anderson JR et al 1983; Simon R et al 1984). PFS and OS estimates will be assessed at specified time points after treatment initiation using Cox proportional hazards model and log-rank test for correlation.

Brief Project Background and Statement of Project Significance:

Patients diagnosed with RRMM have poor prognosis with a 5-year survival rate yet to reach 55% in the US (<https://seer.cancer.gov/statfacts/html/mulmy.html>). The disease remains incurable with current therapies only slowing disease progression, prolonging survival, and minimizing symptoms (Rajkumar and Kumar 2016). Despite the recent introduction of several effective novel agents in RRMM over the past 5 to 10 years, there is still a high unmet medical need for this patient population.

There is a growing body of evidence linking quality of response to improved disease control and outcomes, especially with the introduction of targeted therapies (Harousseau JL et al 2010; Palumbo A et al 2008; Pinedo-Roman M et al 2008; Alegre A et al 2011; Richardson PG et al 2007; Hussein MA et al 2006; Siegel DS et al 2012; Moreau et al 2016; Richardson et al 2005; Niesvizky R et al 2008; Quach H et al 2009; Galaznik A et al 2019; Nooka AK et al 2011). Clinical trials are not typically designed to assess relationships between response and survival, so definitive data are still needed to address gaps in knowledge across treatment settings in MM. In the relapsed/refractory setting, studies have shown associations between depth of response and outcomes, although data are limited.

Daratumumab, a monoclonal antibody directed against CD38, was approved in 2015 in the US and in 2017 in the EU for the treatment of MM patients who have received at least three prior therapies including a PI and an IMiD, or who are double-refractory to these drugs. Efficacy in generating response in RRMM patients have been demonstrated; however, evidence supporting relationships between response to daratumumab and progression and survival outcomes have not yet been fully elucidated. This study will test whether achieving deeper responses with daratumumab-based therapies is linked to longer PFS or longer OS and whether longer PFS correlates with longer OS.

Specific Aims of the Project:

The objectives of this study are to assess whether 1) increasing depths of response is associated with longer PFS and OS and 2) PFS is correlated with OS measures in RRMM patients using individual patient-level data from NCT02076009 and NCT02136134.

Research Methods

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

Individual patient-level data from:

NCT02076009 - Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Relapsed or Refractory Multiple Myeloma
NCT02136134 - Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone (DvD) vs Bortezomib and Dexamethasone (Vd) in Subjects With Relapsed or Refractory Multiple Myeloma

The following clinical and laboratory variables are requested:

1. Date of first treatment
2. OS (1=evt, 0= censor)
3. PFS (1=evt, 0= censor)
4. Treatment arm
5. Line of therapy
6. Baseline ECOG
7. ISS
8. Age
9. Baseline body weight
10. Baseline creatinine
11. Baseline LDH

12. Baseline Hemoglobin (g/L)
13. Baseline Albumin (g/L)
14. Cytogenetics risk status
15. Prior stem cell transplant (auto, allo)
16. Sex
17. IMWG response at each assessment
18. Duration of response
19. Date of MM diagnosis
20. Date of death
21. Date of progression
22. Disease Setting (Relapsed and/or Refractory)
23. Prior therapies (by class, refractoriness if available)

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

PFS and OS (continuous variables)

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

Response based on IMWG response criteria at each assessment (i.e., sCR, CR, VGPR, PR, SD, PD) categorized as CR+, VGPR+, PR+, SD, PD; PFS (continuous), MRD negativity (continuous)

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

Prognostic factors at baseline

Age:

Statistical Analysis Plan:

Individual patient level data from the Phase 3 randomized controlled trials NCT02076009 and NCT02136134 will be used to evaluate associations between response and PFS and OS. Descriptive analysis of baseline characteristics of subjects overall and by treatment arm will be performed, and the distributions of OS and PFS will be estimated using Kaplan-Meier method.

Objective 1: Associations between response and PFS and OS

A multivariate Cox regression analysis for PFS and OS will be conducted separately with response as a time-varying covariate adjusting for prognostic factors, including age, ECOG status, stage at diagnosis, time from diagnosis to treatment, number of prior lines of therapy, prior stem cell transplant, prior therapies, and cytogenetic risk status. Response for each subject will be categorized into the following: ORR (defined as PR+), CR+, VGPR+, SD, and PD. Subjects' response category can change over the treatment course. For example, a subject achieving PR at day 25, CR at day 40 and sCR at day 50 until day 200 would enter the model as PR for days 25-39, CR for days 40-49, and sCR for days 50-200. Unadjusted and adjusted hazard ratios (HRs) and associated 95% confidence intervals (CIs) will be reported for each time-to-event endpoint by treatment arm. Landmark analyses for PFS and OS will also be conducted to confirm the Cox regression analysis and to avoid biases that may occur with classifying subjects by best response during the study (Anderson JR et al 2008; Anderson JR et al 1983; Simon R et al 1984). Time points at 3 months, 6 months, 9 months, and 12 months will be selected with median OS estimated using Kaplan-Meier methods. HRs and 95% CIs will be determined from a Cox proportional hazards model with treatment effect by response category (PR+, CR+, VGPR+, SD, PD) assessed using a 2-sided log rank test.

Objective 2: Associations between PFS and OS

The prognostic value of PFS at 6 months, 12 months, and 18 months for OS after treatment initiation will be evaluated using Cox proportional hazards model stratified by treatment arm for each trial. Log-rank tests between PFS and OS at the patient level will be conducted to estimate the correlation coefficient using a bivariate Copula distribution of the end points over the follow up period with values close to 1 indicating strong correlation between PFS and OS (Burzykowski T et al 2001).

Project Timeline:

Completion is estimated within 1 year of data availability

Completion of contract: April 30, 2021

Obtain de-identified dataset: June-July 2021

Analysis and report submitted to YODA: January 2022

Circulate abstract to YODA targeting EHA 2022: February 2022

Circulate manuscript to YODA targeting hematology journal TBD: Q4 2022

Dissemination Plan:

Results from this study will be used to inform predictions of clinical outcomes from individual treatment responses. This will further inform and support decisions on clinical trial study endpoints and advance our understanding of optimal treatment strategies for RRMM patients, which is a population with high unmet medical need.

Results from this study will be published and made available to the community.

1. Abstract targeting EHA 2022 to YODA: February 2022

2. Draft manuscript to YODA targeting hematology journal TBD: Q4 2022

Target journals are: Blood, American Journal of Hematology, British Journal of Hematology

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