Principal Investigator

First Name: Mellissa
Last Name: Williamson
Degree: PhD
Primary Affiliation: Genentech Inc
E-mail: yongm2@gene.com
Phone number: 650 797 9135
Address:

City: South San Francisco
State or Province: CA
Zip or Postal Code: 94080
Country: USA

General Information

Key Personnel (in addition to PI):
First Name: Mellissa
Last name: Williamson
Degree: PhD
Primary Affiliation: Genentech Inc
SCOPUS ID:

First Name: Hao
Last name: Xu
Degree: MSc
Primary Affiliation: Hoffmann-La Roche
SCOPUS ID:

First Name: Daniela
Last name: Campisi
Degree: BSc
Primary Affiliation: Hoffmann-La Roche
SCOPUS ID:

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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_mw.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_2021-4660_haoxu.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_2021-4660_signed.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

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

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

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

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.

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
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:

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

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

20. Date of death
21. Date of progression
22. Disease Setting (Relapsed and/or Refractory)
23. Prior therapies (by class, refractoriness if available)

Main Outcome Measure and how it 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: <65 year, 65 to 74 years and ?75 years
ECOG: 0, 1-2
Stage: I, II, III
Number of prior lines of therapy: 1-2, 3+
Cytogenetics risk: high, standard
Prior stem cell transplant: yes, no
Sex: male, female
Prior therapies: IMID, PI

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).
Software Used:
R
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 2000
2. Draft manuscript to YODA targeting hematology journal TBD: Q4 2022
Target journals are: Blood, American Journal of Hematology, British Journal of Hematology

Bibliography:

Alegre A, Vicuña I, Aguado B. Safety and efficacy of lenalidomide in relapsed or refractory multiple myeloma. Clin Med Insights Oncol. 2012;6:1-10.

Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. J Clin Oncol. 2008;26(24): 3913-5.

Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol. 1983;1(11):710-9.

Burzykowski T, Molenberghs G, Buyse M, et al. Validation of surrogate end points in multiple randomized clinical trials with failure time end points. J R Stat Soc C. 2001;50:405-422.

Galaznik A, Reich C, Klebanov G, et al. Predicting Outcomes in Patients With Diffuse Large B-Cell Lymphoma Treated With Standard of Care. Cancer Inform. 2019;18:1176935119835538.

Harousseau JL, Dimopoulos MA, Wang M, et al. Better quality of response to lenalidomide plus dexamethasone is associated with improved clinical outcomes in patients with relapsed or refractory multiple myeloma. Haematologica. 2010;95(10):1738-44.

Hussein MA, Baz R, Srkalovic G, et al. Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma. Mayo Clin Proc. 2006;81:889–895.

Moreau P, Weisel KC, Song KW, et al. Relationship of response and survival in patients with relapsed and refractory multiple myeloma treated with pomalidomide plus low-dose dexamethasone in the MM-003 trial randomized phase III trial (NIMBUS). Leuk Lymphoma. 2016;57(12):2839-2847.

Niesvizky R, Richardson PG, Rajkumar SV, et al. The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. Br J Haematol. 2008;143:46–53.

Nooka AK, Behera M, Boise LH, et al. Thalidomide As Maintenance Therapy in Multiple Myeloma (MM) Improves Progression Free Survival (PFS) and Overall Survival (OS): A Meta-Analysis. Blood. 2011;118(21):1855.

Palumbo A, Gay F, Bringhen S, et al. Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. Ann Oncol. 2008;19:1160–1165.

Pineda-Roman M, Zangari M, Haessler J, et al. Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2. Br J Haematol. 2008;140(6):625-34.

Quach H, Mileshkin L, Seymour JF, et al. Predicting durable remissions following thalidomide therapy for relapsed myeloma. Leuk Lymphoma. 2009;50:223–229.

Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc. 2016;91(1):101-19.

Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352:2487–2498.

Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: ?nal time-to-event results of the APEX trial. Blood 2007;110:3557–3560.

Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent car?lzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120:2817–2825.

Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus nonresponder bias. Stat Med. 1984;3(1):35-44.