Principal Investigator

First Name: Susan
Last Name: Bal
Degree: MD
Primary Affiliation: The University of Alabama at Birmingham
E-mail: susanbal@uabmc.edu
Phone number:
Address:
1802 6th Ave S, NP 2540 L
City: Birmingham
State or Province: Alabama
Zip or Postal Code: 35294
Country: USA

General Information

Key Personnel (in addition to PI):

First Name: Susan
Last name: Bal
Degree: MD
Primary Affiliation: University of Alabama at Birmingham
SCOPUS ID: 57210375706

First Name: Smith
Last name: Giri
Degree: MD
Primary Affiliation: University of Alabama at Birmingham
SCOPUS ID: 54417260700

First Name: Kelly
Last name: Godby
Degree: MD
Primary Affiliation: University of Alabama at Birmingham
SCOPUS ID: 56257429800

First Name: Luciano
Last name: Costa
Degree: MD, PhD
Primary Affiliation: University of Alabama at Birmingham
SCOPUS ID: 56973263500

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/yoda_project_coi_form_sg_1.pdf
https://yoda.yale.edu/system/files/sb_yoda_disclosure_1.pdf
https://yoda.yale.edu/system/files/godby_coi_form_for_yoda_project_daratumumb_study_susan_bal_p_04.09.21.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_19.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

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

Research Proposal

Project Title

An individual patient data meta-analysis of daratumumab in the treatment of different cytogenetic subsets of multiple myeloma

Narrative Summary:

The clinical presentation and biological characteristics of multiple myeloma (MM) vary greatly. Daratumumab is an effective anti-myeloma drug that has improved outcomes in relapsed and newly diagnosed MM. But its role in high-risk MM has been unclear largely due to small numbers of such patients in individual clinical trials. Given its cost and side effects, it is important to define its role in patients with high-risk disease to optimally select and sequence therapies. We propose to perform individual patient data metanalysis to understand the benefit of daratumumab in different cytogenetic subsets across the randomized studies available through the YODA project.

Scientific Abstract:

Background: Recurrent cytogenetic abnormalities are the mainstay of prognostic risk assessment in multiple myeloma (MM). Daratumumab is an anti-CD38 monoclonal antibody approved by the FDA for patients with both relapsed and newly diagnosed MM. However, given its cost and side effect profile, it is important to delineate its benefit in traditional as well as more recently defined adverse cytogenetic abnormalities as we try to optimally sequence therapies.
Objective: To understand the benefit of daratumumab in different cytogenetic subsets.
Study Design: This is a systematic review and an individual-patient data meta-analysis to evaluate the effect of daratumumab benefit in different high risk subsets of multiple myeloma. We will perform an individual patient meta-analysis in two stages using the estimates of effect each trial and combining these using random effects methods to derive estimates of the intervention effect.
Participants: Patients treated on three clinical trials (CASTOR, POLLUX AND MAIA) with data submitted to YODA.
Main Outcomes Measures: Progression free survival and overall survival of different cytogenetic subsets in phase 3 trials comparing backbone MM regimens with the same regimen plus daratumumab using individual patient meta analysis.
Statistical Analysis: Individual patient data meta-analysis using a two-stage approach (see more in statistical analysis plan)

Brief Project Background and Statement of Project Significance:

The clinical presentation, biologic behavior and outcomes of patients with multiple myeloma (MM) have great heterogeneity. Recurrent cytogenetic abnormalities are the mainstay of prognostic risk assessment. Daratumumab is an anti-CD38 monoclonal antibody which has improved the patient outcomes and approved by the FDA for patients with both relapsed and newly diagnosed MM. However, given its cost and side effect profile, it is important to delineate its benefit in traditional as well as more recently defined adverse cytogenetic abnormalities as we try to optimally sequence therapies based on disease risk and challenge the one size fits all paradigm. Unfortunately, the numbers of patients of each cytogenetic subset in different studies are too small to draw meaningful conclusions.

Specific Aims of the Project:

• Individual patient meta-analysis to assess the progression free and overall survival of different cytogenetic subsets in phase 3 trials comparing backbone MM regimens with the same regimen plus daratumumab, such that the comparative effectiveness between the 2 groups was primarily caused by the addition of daratumumab. The cytogenetic subsets of interest as are follows:
o t(11;14)
o Gain 1q/Amplification 1q
o R-ISS defined high risk cytogenetics [(t(4;14), t(14;16), del 17p]
• Since the studies were not stratified by these cytogenetic subgroups, the imbalances between the arms could be addressed by multivariate analysis or propensity score to adjust for potential confounders.
• Phase 3 studies reporting comparative effectiveness data stratified by cytogenetic risk status in the primary or subgroup analysis.

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 using only data from YODA Project

Research Methods

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

o Inclusion Criteria
? Adult patients with diagnosis of multiple myeloma treated on a randomized phase III study of backbone regimen + daratumumab vs. backbone regimen
? Availability of Fluorescence in situ hybridization (FISH) data from within 90 days from enrollment of the study

o Exclusion Criteria
? Patients who did not receive at least one cycle of planned therapy
? Patients who did not have FISH data available or not performed

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

The primary outcome is progression free survival (PFS), defined as the time from randomization to the date of first confirmed progression or date of death, whichever occurred earlier. We will quantify associations in terms of hazard ratios (HRs) and 95% CIs. The longest available follow-up results was used to extract the summary effect.

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

• The cytogenetic subsets of interest as are follows:
o t(11;14)
o Gain 1q/Amplification 1q
o Revised international staging system (R-ISS) defined high risk cytogenetics [(t(4;14), t(14;16), del 17p]
• Cytogenetically defined subsets will be assigned as such irrespective of the method used in the study and the proportion of cells exhibiting the cytogenetic abnormality.

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

• Overall survival (OS), defined as the time of randomization to date of death from any cause.
• Overall response rate
• Socio-demographic characteristics of the study population including
- Age
- Sex
- Race/Ethnicity. We will use a composite variable for self-reported race/ethnicity, classified as Hispanic, non-Hispanic white, non-Hispanic African American, and other (Pacific Islander, American-Indian, or Alaska Native)
- Eastern Cooperative Oncology Group (ECOG) performance score
• Disease specific characteristics including
- M protein isotype
- International Staging System (ISS)
- Serum creatinine
- Lactate dehydrogenase (LDH)
- Hemoglobin
- Beta 2 microglobulin
- Albumin
- Calcium
- Karyotype
- Extramedullary disease

Statistical Analysis Plan:

We will use an individual meta-analysis (IPD) approach for this analysis. First the risk of bias of individual studies included in this analysis will be done using the Cochrane Risk of Bias tool assessing domains including randomization sequence, allocation concealment, blinding assessment, outcome reporting as well as assessment of the quality of time to event data. Primary trial authors may be contacted for additional clarifications if necessary. We will conduct this IPD meta-analysis using a two-stage approach combining data while preserving participants' trial membership. In the first stage, estimates of effect will be derived from the IPD for each trial and in the second stage, these are combined using random effects methods (Dersimonian and Laird) to derive estimates of the intervention effect, analogous to aggregate data meta-analysis, to account for any differences in effect across trials (heterogeneity). We will assess heterogeneity using the I2 statistic and Cochrane's Q function. Forrest plots will be used to graphically summarize the aggregate results.
Finally, we will explore whether intervention effects vary by trial or participant level characteristics using subgroup analysis, whereby intervention effects are compared between groups of trials, or meta-regression approach where the change in overall intervention effect in relation to trial characteristics is investigated.
Analysis will be done using R and STATA using the admetan package for IPD metanalysis.
Software Used:
STATA
Project Timeline:

YODA project approval/data availability to analysis - 4 weeks
Data analysis to abstract preparation - 4 weeks
Abstract preparation to manuscript submission - 8 weeks

Dissemination Plan:

The results from the data analysis will be shared with YODA and thereafter abstract will be submitted to the Annual Society of Hematology meeting (ASH) 2021. The manuscript will then be simultaneously be prepared for submission by 11/2021 for consideration of publication in high impact medical journals such as Jama Oncology, Leukemia or Lancet Hematology.

Bibliography:

1. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28(5):1122-1128. doi:10.1038/leu.2013.313

2. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(15):3412-3420. doi:10.1200/JCO.2005.04.242
3. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(26):2863-2869. doi:10.1200/JCO.2015.61.2267
4. Heuck CJ, Qu P, van Rhee F, et al. Five gene probes carry most of the discriminatory power of the 70-gene risk model in multiple myeloma. Leukemia. 2014;28(12):2410-2413. doi:10.1038/leu.2014.232
5. Bergsagel PL, Kuehl WM. Molecular pathogenesis and a consequent classification of multiple myeloma. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(26):6333-6338. doi:10.1200/JCO.2005.05.021
6. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis. JAMA Oncol. 2017;3(1):28-35. doi:10.1001/jamaoncol.2016.3160
7. Genetics and Cytogenetics of Multiple Myeloma | Cancer Research. Accessed February 16, 2021. https://cancerres.aacrjournals.org/content/64/4/1546
8. Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23(12):2210-2221. doi:10.1038/leu.2009.174
9. Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. Blood Cancer J. 2015;5(10):e365-e365. doi:10.1038/bcj.2015.92
10. Abdallah N, Rajkumar SV, Greipp P, et al. Cytogenetic abnormalities in multiple myeloma: association with disease characteristics and treatment response. Blood Cancer J. 2020;10(8):1-9. doi:10.1038/s41408-020-00348-5
11. Ross FM, Chiecchio L, Dagrada G, et al. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. Haematologica. 2010;95(7):1221-1225. doi:10.3324/haematol.2009.016329
12. Giri S, Huntington SF, Wang R, et al. Chromosome 1 abnormalities and survival of patients with multiple myeloma in the era of novel agents. Blood Adv. 2020;4(10):2245-2253. doi:10.1182/bloodadvances.2019001425
13. D'Agostino M. Impact of Gain and Amplification of 1q in Newly Diagnosed Multiple Myeloma Patients Receiving Carfilzomib-Based Treatment in the Forte Trial. In: ASH; 2020. Accessed February 15, 2021. https://ash.confex.com/ash/2020/webprogram/Paper137060.html
14. Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia. 2019;33(1):159-170. doi:10.1038/s41375-018-0196-8
15. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. J Clin Oncol. 2019;37(14):1228-1263. doi:10.1200/JCO.18.02096
16. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015;373(13):1207-1219. doi:10.1056/NEJMoa1506348
17. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018;378(6):518-528. doi:10.1056/NEJMoa1714678
18. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. The Lancet. 2019;394(10192):29-38. doi:10.1016/S0140-6736(19)31240-1
19. Voorhees PM, Kaufman JL, Laubach JP, et al. Daratumumab, Lenalidomide, Bortezomib, & Dexamethasone for Transplant-eligible Newly Diagnosed Multiple Myeloma: GRIFFIN. Blood. Published online April 23, 2020:blood.2020005288. doi:10.1182/blood.2020005288
20. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(8):754-766. doi:10.1056/NEJMoa1606038
21. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(14):1319-1331. doi:10.1056/NEJMoa1607751
22. Giri S, Grimshaw A, Bal S, et al. Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients With High-risk Cytogenetic Factors: A Systematic Review and Meta-analysis. JAMA Oncol. Published online September 24, 2020. doi:10.1001/jamaoncol.2020.4338
23. Lakshman A, Alhaj Moustafa M, Rajkumar SV, et al. Natural history of t(11;14) multiple myeloma. Leukemia. 2018;32(1):131-138. doi:10.1038/leu.2017.204
24. Bal S. Redefining the Prognostic Significance of t(11;14) Multiple Myeloma. In: ASH; 2020. Accessed February 16, 2021. https://ash.confex.com/ash/2020/webprogram/Paper138888.html
25. Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. Published online October 29, 2020. doi:10.1016/S1470-2045(20)30525-8
26. Shaughnessy JD Jr, Qu P, Usmani S, et al. Pharmacogenomics of bortezomib test-dosing identifies hyperexpression of proteasome genes, especially PSMD4, as novel high-risk feature in myeloma treated with Total Therapy 3. Blood. 2011;118(13):3512-3524. doi:10.1182/blood-2010-12-328252

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

27. Bochtler T, Hegenbart U, Kunz C, et al. Translocation t(11;14) Is Associated With Adverse Outcome in Patients With Newly Diagnosed AL Amyloidosis When Treated With Bortezomib-Based Regimens. J Clin Oncol. 2015;33(12):1371-1378. doi:10.1200/JCO.2014.57.4947