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General Information

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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_for_data_requestors_2019_5.docx
https://yoda.yale.edu/system/files/raul_yoda_coi_form_for_data_requestors_2019.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. NCT01615029 - DARA-GEN503 - An Open Label, International, Multicenter, Dose Escalating Phase I/II Trial Investigating the Safety of Daratumumab in Combination With Lenalidomide and Dexamethasone in Patients With Relapsed or Relapsed and Refractory Multiple Myeloma
4. NCT00574288 - 54767414GEN501 - Daratumumab (HuMax®-CD38) Safety Study in Multiple Myeloma - Open Label, Dose-escalation Followed by Open Label, Single-arm Study

5. [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](#)
6. [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

Outcomes with Early versus Late Response to Daratumumab in Patients with Refractory/Relapsed or Newly Diagnosed Multiple Myeloma

Narrative Summary:

While achieving rapid remission after starting chemotherapy has long been recognized as a good prognostic sign in acute leukemia, it is still controversial in multiple myeloma (MM) whether early responders have better outcomes. Daratumumab is a new class of medication that has been increasingly used in patients with MM. However, the association between its kinetic pattern (early vs late response) and disease course remains unexplored. In this study, we aim to compare survival outcomes between early and late responders to daratumumab. The results of the study will help clinicians better predict response and disease progression in patients with MM.

Scientific Abstract:

Background: It is controversial in multiple myeloma (MM) whether early or late responders to conventional regimens have similar clinical outcomes. Daratumumab (DARA) is a humanized anti-CD38 antibody that has been increasingly used in newly diagnosed MM (NDMM) or relapsed/refractory MM (RRMM). The association between DARA's kinetic pattern (early vs late response) and disease course remains unexplored.
Objective: To compare the clinical outcomes of patients with NDMM or RRMM who responded early versus late to DARA, and identify factors associated with early and late response.
Study design: Using individual participant data (IPD) obtained from YODA, patients with MM achieving very good partial response (VGPR) or better will be divided into the early and late response groups based on the median time to best response. Progression-free survival (PFS) and duration of response (DOR) between the two groups will be compared. In addition, clinical factors associated with early and late response will be explored.
Participants: Patients with either NDMM or RRMM receiving DARA-based regimens.
Main outcome measures: PFS and DOR differences between early and late responders.
Statistical analysis: The difference of PFS will be compared using landmark analysis and time-dependent covariate analysis. Difference of duration of response (DOR) will be compared using Kaplan-Meier methods. Clinical factors associated with early and late response will be explored using univariate and multivariable logistic regression. Subgroup analysis and sensitivity analysis will also be performed.

Brief Project Background and Statement of Project Significance:

Rapid response after the initiation of chemotherapy has long been recognized as a favorable prognosticator in patients with acute leukemia (1). However, it is still controversial in multiple myeloma (MM) regarding the association between rapidity of response and survival outcomes. Indeed, for patients receiving conventional regimens, few studies found a rapid response to treatment was associated with a better survival (2), while some studies found early and late responders have no differences regarding progression-free survival (PFS) or overall survival (OS) (3, 4), and other studies found patients who responded late actually had better PFS and duration of response (DOR) (5-7). It has been postulated that rapid response in MM may be a result of targeting highly proliferative MM cells resulting in rapid selection of resistant clones, which leads to poor outcomes. Indeed, patients

with high-risk cytogenetics and higher stage of MM are more likely to achieve early response (4). Daratumumab, a humanized IgG1k anti-CD38 monoclonal antibody, has achieved deeper response and better survival than conventional therapies in patients with either newly diagnosed MM (NDMM) or relapsed/refractory MM (RRMM); it has revolutionized the treatment for MM (8). However, the disease response kinetics of daratumumab remains unexplored. It is unclear in the era of daratumumab whether early and late responders have different clinical outcomes.

The results of the study will help clinicians better recognize the response pattern of daratumumab and predict long-term outcomes based on early clinical course.

Specific Aims of the Project:

Specific Aim 1: Among patients with MM achieving very good partial response (VGPR) or better, compare progression-free survival (PFS) and duration of response (DOR) between early and late responders to daratumumab.
Hypothesis to Aim 1: Late responders will have longer PFS and DOR.
Specific Aim 2: Explore baseline clinical characteristics significantly associated with early and late response to daratumumab.
Hypothesis to Aim 2: Certain high-risk characteristics of MM will be associated with early response to daratumumab.
Specific Aim 3: Compare response-kinetics pattern between daratumumab regimens and non-daratumumab regimens.
Hypothesis to Aim 3: Patients receiving daratumumab will have more late responders.

What is the purpose of the analysis being proposed? Please select all that apply.
Research on comparison group

Research Methods

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

Data Source: IPD from the following trials
1. NCT00574288: Phase 1 daratumumab dose-escalation in RRMM
2. NCT01615029: Phase 1/2 DRd in RRMM
3. NCT01985126: Phase 2 daratumumab monotherapy in RRMM
4. NCT02076009: Phase 3 DRd vs Rd in RRMM
5. NCT02136134: Phase 3 DVd vs Vd in RRMM
6. NCT02252172: Phase 3 DRd vs Rd in NDMM
Inclusion Criteria
1. Adult patients with MM receiving standard dosing (16mg/kg) and schedule (once weekly x 8 doses, then every 2 weeks x 8 doses, then every 4 weeks) of daratumumab
Exclusion Criteria
1. Patients crossed over to the other group
2. Patients received different dosing than the standard dosing of daratumumab
3. Patients received different dosing schedule than the standard dosing schedule of daratumumab

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

• The main outcome measure will be progression-free survival (PFS) and duration of response (DOR)
• PFS is defined as the length of time from treatment initiation to disease progression or death of any cause.
• DOR is defined as the length of time from the first documentation of very good partial response (VGPR) or better to disease progression or death of any cause.

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

1. For Specific Aim 1: the main predictor is early versus late response. The early and late response group will be determined by the median time to VGPR or better.
2. For Specific Aim 2: the main predictors are patients' baseline characteristics, which include demographic information such as age, sex, race, and clinical characteristics, such as cytogenetics, performance status, M-

protein type and level, beta-2 microglobulin level, albumin level, LDH level, and previous lines of treatment.
3. For specific Aim 3: the main predictor is the use of daratumumab.

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

1. Time of death
2. Time to last follow up

Statistical Analysis Plan:

1. Aim 1: To address immortal-time bias, two analytic methods will be performed to compare PFS between early and late responders. First, a landmark analysis will be performed, in which arbitrary cut-offs of 6 and 9 months will be selected and PFS will be calculated starting from the cut-off points. Then a time-dependent Cox regression analysis will be performed to see if early and late responses are associated with PFS. To compare DOR between the two groups, Kaplan-Meier method will be used.
2. Aim 2: Univariate logistic regression analysis will be performed, with variables including age, sex, race, high-risk cytogenetics, International Staging System (ISS) stage, LDH level, and previous lines of therapy. Variables significantly associated with early versus late response (p<0.05) will be chosen for multivariable logistic regression analysis.
3. Aim 3: Similar to Aim 1, but subgroup analysis between daratumumab and non-daratumumab regimens will be performed.
4. For sensitivity analysis, the early and late response cut-off point will be adjusted to 2 months and 4 months according to previous studies. Then for a second sensitivity analysis, only patients achieving complete response (CR) or better will be included for PFS and DOR analysis.
Software Used:
RStudio
Project Timeline:

Once study is approved and data access provided (assuming by July 2021), our key milestones dates are:
Project start: July 1, 2021
Data collection and analysis completion: September 1, 2021
Manuscript drafted and submitted for publication: October 1, 2021
Date results reported back to YODA: November 1, 2021

Dissemination Plan:

We anticipate generating one manuscript from the project. The target audience will be hematologists/oncologists who treat patients with multiple myeloma.

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