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Requires Data Access? No

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?: PubMed

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/11/Marta-Hidalgo-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2023/11/Yoda-Proyect-Inma.pdf
https://yoda.yale.edu/wp-content/uploads/2023/11/ADRIANA-ONOS-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2023/11/YODA-Merche.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. NCT02195479 - 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
2. NCT02252172 - 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
3. NCT03412565 - A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination With Standard Multiple Myeloma Treatment Regimens

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

Research Proposal

Project Title

Prospective Assessment of ISS-R2 as a Prognostic Indicator in Patients with Newly Diagnosed Multiple Myeloma in the Anti-CD38 Era

Narrative Summary:

The patients with newly diagnosed with multiple myeloma (NDMM) exhibit varied outcomes, with around 60% falling into the intermediate-risk category based on the Revised International Staging System (R-ISS). Recent evidence identifies chromosome 1q gain/amplification (1q+) as a negative prognostic factor. The Second Revision of the International Staging System (R2-ISS), introduced in 2022 and validated across multiple multiple myeloma (MM) cohorts, highlights the influential roles of 1q21 gain, alone or in conjunction with other cytogenetic abnormalities. However, this prognostic score lacks validation in patients undergoing anti-CD38-based regimens.

The primary objectives of this study is to evaluate the R2-ISS score's prognostic capability for predicting overall survival (OS) and progression-free survival (PFS) in newly diagnosed multiple myeloma (NDMM) patients undergoing first-line treatment with anti-CD38-based regimens from the YODA Project Database.

Scientific Abstract:

BACKGROUND:
Multiple myeloma (MM) is a complex malignancy characterized by highly diverse tumor biology, particularly involving cytogenetic abnormalities. As a result, MM patients exhibit a wide spectrum of clinical features, therapeutic responses, and outcomes. The International Staging System (ISS), established in 2005 and later updated in 2015 (as revised International Stagin System, R-ISS), has been a pivotal tool in predicting the prognosis of MM patients. Despite its widespread use, certain limitations have surfaced, such as the varied outcomes within the R-ISS II category and the inadequate consideration of factors like 1q gain/amplification and concurrent high-risk cytogenetic abnormalities (HRCAs).

Recognizing these limitations, various novel prognostic scoring systems have been introduced, with the latest being the second revision of ISS (R2-ISS) by the European Myeloma Network (EMN). Notably, the R2-ISS identifies five high-impact risk variables—ISS III, ISS II, del(17p), high lactate dehydrogenase (LDH), t(4;14), and 1q+ (1q gain or amplification). It categorizes patients into four risk groups (I to IV) based on their cumulative scores.

In two independent cohorts, R2-ISS demonstrated the ability to effectively stratify newly diagnosed MM (NDMM) patients into distinct risk groups, showing significant differences in both Overall survival (OS) and profression free surivival (PFS). The stratification remained meaningful across different upfront treatments, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), or a combination of both. Notably, the R2-ISS excelled in discerning OS and PFS among R-ISS II patients, underscoring its valuable role in reclassifying this large and heterogeneous subgroup of NDMM patients.

It is essential to highlight that the ISS-R2 has not undergone validation in patients who have received anti-CD38 or immunotherapy. This highlights the need for further research and validation studies to assess the applicability and reliability of the R2-ISS in this specific patient population, providing a comprehensive understanding of its prognostic value in the ever-evolving landscape of multiple myeloma management.

OBJECTIVE
The objective of this study is to assess capacity of the predicting prognostic events of the Revised International Staging System (ISS-R2) in newly diagnosed multiple myeloma (NDMM) patients undergoing first-line treatment with anti-CD38.

STUDY DESIGN:
Retrospective observational study

PARTICIPANTS:
Participants for this study will include NDMM patients who are undergoing treatment with anti-CD38-based regimens enrolled in clinical trials accessible through the YODA project.

PRIMARY OUTCOME
Examine the Correlation Between ISS-R2 Risk Categories and Clinical Outcomes: In our manuscript we prupose to investigate the association between risk categories delineated by the ISS-R2 and clinical outcomes, encompassing overall survival (OS) and progression-free survival (PFS) in NDMM treated with daratumumab.
SECONDARY OUTCOME
Conduct External Validation Analysis: Validate the results achieved with the ISS-R2 through external validation analysis to ensure their robustness and applicability beyond the initial study population
Assess the discriminative capacity of the new score compared to previous ones within the patient cohort

STATISTICAL ANALYSIS
The statistical analysis will include a descriptive analysis of the demographic and clinical characteristics within the study population, accompanied by a evaluation of ISS, ISS-R and R2-ISS risk scores. OS is defined as the time from the date of the initial therapy to the time of death or last follow-up. PFS is defined as the time from diagnosis to the time of first documented disease progression, death or last follow-up. Survival analysis will be plotted using Kaplan-Meier method and compared using the two-sided log-rank test. A p-value <0.05 will be considered statistically significant.
Multivariate regression analysis will be employed to adjust and validate R2-ISS risk scores in relation to other prognostic variables. Concordance index (C-index) calculations will gauge the discriminative capacity of R2-ISS in predicting prognostic events.

Brief Project Background and Statement of Project Significance:

The integration of anti-CD38 monoclonal antibodies (mAbs) into both triplet and quadruplet regimens has showcased the transformative potential of immunotherapy in enhancing response rates, depth of response as negative minimal residual disease, PFS, and overall survival in NDMM patients, particularly those with high cytogenetic risk.
This positive impact extends to patients facing high cytogenetic risk.
Consequently, there arises a critical imperative to thoroughly evaluate the predictive capacity of

prognostic scores as R2-ISS within the landscape of immunotherapy.

Specific Aims of the Project:

The main aim of this study is to assess the predictive capacity of the Revised International Staging System (ISS-R2) in predicting prognostic events as OS and PFS in NDMM patients undergoing first-line treatment with anti-CD38.
As a secondary objective, the study aims to assess whether the new score improves predictive accuracy for overall survival and progression-free survival compared to previous scores (ISS, R-ISS) within the patient cohort.

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

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:

INCLUSION CRITERIA
Clinical characteristics:
- 18 years-old or older
- NDMM
- first line with antiCD38 based- treatment included in the YODA project Database.
- ISS and ISS-R at diagnosis available
- High risk chromosomal abdormalities by FISH available
- Serum LDH and albumin levels at diagnosis available
- OS and PFS available
- Response status at the moment of the analysis avaiable (according to the IMWG 2016 criteria)

ESCLUSION CRITERIA
Patients for whom the data required for the study are not available

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

PRIMARY OUTCOMES::
- OS: OS is defined as the time from the date of the initial therapy to the time of death or last follow-up.
- PFS: PFS is defined as the time from diagnosis to the time of first documented disease progression, death or the last of follow-up.

SECONDARY OUTCOMES:
- Response status according to the IMWG 2016 criteria

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

Age
Date of diagnosis
ISS

R-ISS
LDH serum and albumin levels at diagnosis
High risk chromosomal abdormalities (specify)
Presence of del(17p), t(4;14) or 1q+
Date of initiation of therapy
Best response achieved during treatment
Date of best response
Date of last follow up
Progression disease (Y/N)
Date of progression
Death (Y/N)
Date of death
Multiple myeloma response status at last follow-up

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

Type of MM (igG, IgM, igD, IgE)
Regimen used (D-VMP, DRd...)

Statistical Analysis Plan:

The statistical analysis will encompass a descriptive examination of demographic and clinical characteristics within the study population, along with an assessment of individual patient scores, including ISS, ISS-R, and R2-ISS risk scores. Survival analysis will be plotted using Kaplan-Meier method and compared using the two-sided log-rank test. A p-value <0.05 will be considered statistically significant.
To assess the discriminatory power of the R2-ISS, the analysis will include the application of the C-statistic or Area under the Receiver Operating Characteristic (ROC) curve.

Software Used:

R

Project Timeline:

Anticipated project start date : 15 DEC 2023
analysis completion date: 30 JAN 2024
Date manuscript drafted: 28 FEB 2024
Date results reported back to the YODA Project. 30 MAR 2024
first submitted for publication: 1 MAY 2024

Dissemination Plan:

The target audience for these manuscripts encompasses the scientific and medical communities, particularly hematologists, oncologists, and researchers specializing in multiple myeloma. We expect the study manuscripts to contribute valuable insights to the field of prognostic assessment in multiple myeloma and guide clinical decision-making.

As for potential suitable journals for submission, we plan to target reputable publications with a focus on hematology, oncology, and prognostic modeling. Journals such as the Journal of Clinical Oncology, Annals of Hematology, Blood, and Haematologica are under consideration due to their high impact factor and relevance to our research scope.

Bibliography:

1. D’Agostino M, Cairns DA, Lahuerta JJ, et al. Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within

the HARMONY Project. J Clin Oncol. 2022 Oct 10;40(29):3406-3418. doi: 10.1200/JCO.21.02614. Epub 2022 May 23. Erratum in: J Clin Oncol. 2022 Dec 1;40(34):4032. PMID: 35605179.

2. Guo W, Zhan A, Mery DE, Munshi MN, et al. Application of R2-ISS risk stratification to patients with multiple myeloma treated with autologous stem cell transplants at UAMS. Blood Adv. 2023 Nov 14;7(21):6676-6684. doi: 10.1182/bloodadvances.2023011096. PMID: 37756524; PMCID: PMC10637884.

3. Yang P, Zhou F, Dong Y, Gao G, Xue H, et al. The R2-ISS in a Multicenter Cohort of Chinese Patients With Newly Diagnosed Multiple Myeloma. Hemasphere. 2023 Mar 24;7(4):e857. doi: 10.1097/HS9.0000000000000857. PMID: 36999007; PMCID: PMC10043562.

4. Minguela A, Vasco-Mogorrón MA, Campillo JA, et al. Predictive value of 1q21 gain in multiple myeloma is strongly dependent on concurrent cytogenetic abnormalities and first-line treatment. Am J Cancer Res. 2021 Sep 15;11(9):4438-4454. PMID: 34659897; PMCID: PMC8493371.