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ORAL ABSTRACTS

905.OUTCOMES RESEARCH-LYMPHOID MALIGNANCIES

Performance of Newer Staging Systems for Myeloma in a Contemporary, Large Cohort of Patients in the United States

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INTRODUCTION The most widely used multiple myeloma (MM) staging system, the Revised International Staging System (R-ISS), is based on lactate dehydrogenase (LDH), albumin, high-risk genetic markers by FISH, and beta-2 microglobulin (B2M). However, it does not account for additional risk impacted by multiple genetic abnormalities, or the risk imparted by presence of gain of chromosome 1q, and most patients are staged as R-ISS Stage 2.
Two new staging systems, the Mayo Additive Staging System (MASS), and the Second Revision of the International Staging System (R2-ISS) have been recently proposed. A comparison of the performance of these two systems has not previously been done. We aimed to externally demonstrate the application of these staging systems and compare their performances in a large, contemporary cohort of patients in the United States.

METHODS We conducted a retrospective cohort study using the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction and originating from approximately 280 US cancer clinics (~800 sites of care). The study included newly diagnosed MM patients initiating treatment between January 1, 2016 and October 1, 2022. We used the Kaplan-Meier method to evaluate real-world overall survival (rwOS) and patients were followed from first-line treatment initiation (index date) until the first of death, end of the study period or last recorded activity. The log-rank test to compare survival curves across derived stages. Multivariable analysis was conducted using stratified Cox models to account for non-proportional hazards by age with covariate adjustment for race/ethnicity, sex, practice type (academic or community) and diagnosis year (2016-2019 vs 2020-2022). Discrimination and calibration were evaluated in crude models using Harrell's c-index and the Hosmer-Lemeshow goodness-of-fit test, respectively.

RESULTS There were 497 patients with MM included. Patient characteristics are listed in Panel A. The distribution of patients across R-ISS stages were as follows, 24%, 63% and 13% for Stage 1, 2 and 3 respectively. rwOS differed across R-ISS stage (log-rank $p = 0.0006$) and the median OS (OS) was not reached (NR), 63, and 37 months for R-ISS stage 1, 2, and 3, respectively.

Patients were more evenly categorized across MASS stages 34%, 35% and 31% for MASS 1, 2, and 3, respectively. The corresponding survival curves were significantly different ($p < 0.0001$), with associated mOS of 77, 61 and 45 months for MASS stages 1, 2, and 3, respectively.
R2-ISS includes four risk categories (stages I-IV) and in our cohort, 20% ($n = 100$) were stage I (low), 126 (25%) were stage II (low-intermediate), 229 (46%) were stage III (intermediate), and 42 (9%) were stage IV (high). Survival across stages were significantly different ($p<0.0001$), though the survival curves for low and low-intermediate, and intermediate-high and high,

were clustered, suggesting comparable outcomes in stages I-II and stages III-IV. mOS for R2-ISS stages I, II, III, and IV was NR, 69, 50 and 51 months respectively (Panel B).
In fully adjusted analyses, as compared to MASS I, the hazards of death were 2.0 (95% CI 1.3-3.2) for MASS II and 2.7 (1.7-4.2) for MASS III. The hazards of death were similar for R2-ISS low and low-int (HR for low-int vs low: 1.2 [0.7, 2.3]). As compared to R2-ISS low, the hazards of death were similarly higher for int-high and high (HRs: 2.4 [1.4, 4.1] and 2.6 [1.3, 5.2], respectively). Discrimination and calibration were similar across all staging systems (c = 0.6, and Hosmer-Lemeshow p>0.05 for all three staging systems).

CONCLUSION Application of contemporary MM staging systems in a large cohort of US patients shows that they are prognostic for OS in MM. MASS demonstrated a greater separation for OS across stages, whereas R2-ISS intermediate-high and high were largely overlapping. Although our results demonstrate similar accuracy and reliability of MASS and R2-ISS, the discrimination of patients across different stages seen with the newer staging systems, as opposed to R-ISS, calls for greater use of these newer staging systems in routine clinical practice.

Disclosures Fonseca: *Antegene:* Membership on an entity's Board of Directors or advisory committees; *Regeneron:* Consultancy; *Oncotracker:* Membership on an entity's Board of Directors or advisory committees; *Millenium:* Consultancy; *Binding Site:* Consultancy; *Janssen:* Consultancy; *Juno:* Consultancy; *Merck:* Consultancy; *Pfizer:* Consultancy; *Aztrazenica:* Consultancy; *Kite:* Consultancy; *Adaptive Biotechnologies:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Consultancy; *BMS (Celgene):* Consultancy; *Takeda:* Consultancy; *AMGEN:* Consultancy; *FISH:* Patents & Royalties: FISH; *AZBio:* Membership on an entity's Board of Directors or advisory committees; *Bayer:* Consultancy; *Pharmacyclics:* Consultancy; *Caris Life Sciences:* Membership on an entity's Board of Directors or advisory committees; *Adaptive Biotechnologies:* Consultancy; *AbbVie:* Consultancy. **Calip:** *Flatiron:* Current Employment; *Roche:* Current equity holder in publicly-traded company. **Wang:** *Flatiron:* Current Employment; *Roche:* Current equity holder in publicly-traded company. **Parrinello:** *Flatiron Health:* Consultancy; *Clue by Biowink:* Consultancy; *Evidation Health:* Consultancy; *EQRx:* Consultancy; *Roche:* Current equity holder in publicly-traded company; *Medicus Economics:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *Omada Health:* Consultancy; *Plinth:* Consultancy; *TTI Health:* Consultancy. **Sborov:** *Gilead:* Research Funding; *Arcellx:* Consultancy, Research Funding; *Bioline:* Consultancy, Research Funding; *Pfizer:* Consultancy, Research Funding; *BMS:* Consultancy; *Abbvie:* Consultancy; *Sanofi:* Consultancy, Research Funding; *Janssen:* Consultancy, Research Funding; *Amgen:* Research Funding; *GSK:* Consultancy, Research Funding; *Cantex:* Research Funding; *RocheX:* Research Funding.

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Panel A. Baseline characteristics of newly diagnosed multiple myeloma patients at initiation of first-line therapy

	Overall cohort (N = 497) n	(%)
Age, years		
Median (IQR)	70	(62-76)
Sex, n (%)		
Female	234	(47.1)
Male	263	(52.9)
Practice type		
Community	409	(82.3)
Academic	88	(17.7)
ECOG PS[1]		
0	157	(31.6)
1	177	(35.6)
2-4	84	(16.9)
Unknown	79	(15.9)
First-line treatment type[2]		
Doublet	69	(13.9)
Triplet	336	(67.6)
Quad	53	(10.7)
Other	39	(7.8)
ASCT		
≤1 year post-initiation	150	(30.2)
>1 year post-initiation	17	(3.4)
Not transplanted	330	(66.4)
High-risk cytogenetics		
Translocation (4;14)	47	(9.5)
Translocation (14;16)	28	(5.6)
Translocation (14;20)	9	(1.8)
1q gain / amplification	167	(33.6)
Deletion 17p	46	(9.3)

Abbreviations: ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range

1. ECOG PS was identified as the value closest to the index date (within 30 days before and up to 7 days after the index date)
2. Patients receiving either monotherapy or a clinical study drug were categorized as "Other"

Panel B. Kaplan-Meier survival curves by R2-ISS stage

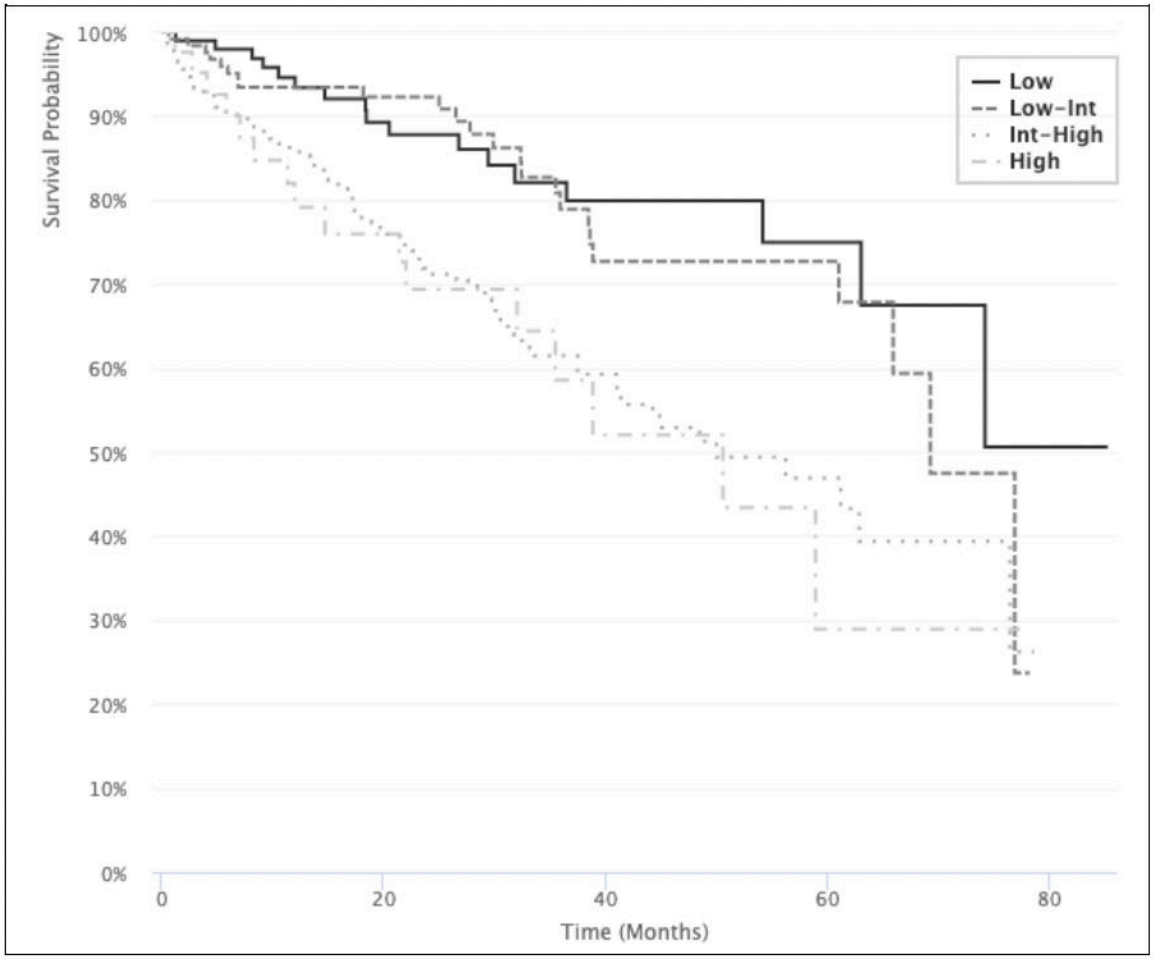

Figure 1