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Real-world outcomes of newly diagnosed multiple myeloma patients treated with front-line daratumumab bortezomib lenalidomide and dexamethasone

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Authors' Contributions

Parrondo and Menezes designed the study. Parrondo and Menezes wrote the manuscript. Sledge performed the statistical analysis. Menezes, Nayyar, Yadav collected the data. All authors analyzed the data for the study. All authors critically revised the manuscript and approved the final version.

Conflict of Interest

Parrondo serves on the advisory board for Sanofi Aventis, Johnson and Johnson, Bristol Myers Squibb, and Astra Zeneca and has received research funding from Bristol Myers Squibb Foundation, BeOne Medicines USA and GlaxoSmithKline. **Ailawadhi** has provided consultancy for Celgene, Amgen, Janssen and Takeda, and has received research funding from Pharmacyclics, Cellectar and Janssen. **Bergsagel** served as consultant: Oncopeptidfes. Salarius, Radmetrix, Omeros, CellCentric, AbbVie, Pfizer. **Chhabra** honoraria from Sanofi, Ascentage Pharma, Sobi, Legend Biotech, BMS and research funding from Johnson & Johnson, Cynata Therapeutics, C4 Therapeutics, Abbvie, Ascentage Pharma, AstraZeneca, Cullinan Therapeutics**; Chanan-Khan** has received research funding from Xencor Pharmacyclics, Merck, Janssen, Ascentage and Millennium. **Kapoor** received research funding from Takeda Pharmaceuticals, Celgene, and Amgen. **Dispenzieri** received research funding from Celgene, Millennium Pharmaceuticals, Pfizer, and Janssen and received a travel grant from Pfizer. **Gertz** served as a consultant for Millennium Pharmaceuticals and received honoraria from Celgene, Millennium Pharmaceuticals, Onyx Pharmaceuticals, Novartis, GlaxoSmithKline, Prothena, Ionis Pharmaceuticals, and Amgen. **Fonseca** performs consulting for: AbbVie, Adaptive, Amgen, Apple, BMS/Celgene, GSK, Janssen, Karyopharm, Pfizer, RA Capital, Regeneron, Sanofi. Scientific Advisory Board: Caris Life Sciences. Board of Directors: Antengene. Patent for FISH in MM - ~$2000/year. **Kumar** Consulting or Advisory Role: Takeda, Janssen Oncology, Genentech/Rocher, Abbvie, BMS/Celgene, Pfizer, Regeneron, Sanofi, K36 Therapeutics; travel, accomodation and expenses: Abbvie, Pfizer; Research funding: Takeda, Abbvie,

Novartis, Sanofi, Janssen Oncology, MedImmune, Roche/Genentech, CARsgen Therapeutics, Allogene Therapeutics, GSK, Regeneron, BMS/Celgene. **Leung** serves on an advisory board for Takeda Pharmaceuticals. **Lin** serves on advisory board role for Janssen, Sanofi, BMS, Regeneron, Genentech, Tesserae, Legend, NexT Therapeutics, steering committee for Janssen, Kite/Gilead, research funding from Janssen, BMS, scientific advisory board for Nonimmune, Caribou and sata safety monitor board for Pfizer. The remaining authors declare no competing financial interests.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

To the editor:

The phase III PERSEUS trial compared daratumumab (dara), bortezomib (bor), lenalidomide (len), and dexamethasone (DVRd) to VRd in newly diagnosed multiple myeloma (NDMM) patients that were autologous stem cell transplant (ASCT) eligible and demonstrated unprecedented complete response rates, minimal residual disease negativity (MRD-) rates, and progression free survival (PFS) favoring DVRd over VRd (1). The PERSEUS trial included twice weekly bor administration, DVRd consolidation for two cycles after ASCT, and dual agent post-ASCT maintenance with dara and len (DR). Little is known about the efficacy and administration patterns of DVRd in real world (RW) practice including subsequent treatment after progression on DVRd. In this retrospective analysis, we aim to evaluate the RW efficacy and the clinical outcomes of NDMM patients treated with DVRd across the tri-site Mayo Clinic Comprehensive Cancer Center (MCCC).

We retrospectively analyzed the medical records of patients treated with DVRd between June 2018 and June 2024 at the MCCC. Descriptive statistics were used to describe patient characteristics. Categorical variables were compared with Chi-square tests and continuous variables were compared with t tests. Outcomes were estimated using the Kaplan–Meier method. IMWG criteria was used for response assessment and MRD was evaluated with a minimum sensitivity of 1 in 10^5 nucleated cells or higher as per IMWG criteria (2). Ultra high-risk myeloma was defined as per the new IMS/IMWG consensus recommendation (3). The study protocol and all amendments were reviewed and approved by the Institutional Review Board at Mayo Clinic Florida (IRB # 23-001194) as an IRB-exempt study. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the principles originating from the Declaration of Helsinki.

464 patients were included; baseline characteristics are shown in **Supplemental Table 1**. Starting len dose was 25mg in 356 (76.7%) patients, 15 mg in 40 patients (8.6%) and ≤10mg in 65 patients (14.0%). 399 (86%) patients received bor 1x per week and 63 (14%) 2x per week, 91 patients received 1-2 cycles of a different regimen prior to DVRd due to hospitalization (n=23), renal insufficiency (RI) (n=38), poor performance status

(n=6), other (n=34). 315 (67.9%) patients underwent ASCT. The median number of induction cycles was 5; 4 (1-16) for patients who underwent ASCT and 6 (1-28) for patients who did not. 42 patients (13%) received post-ASCT consolidation with DVRd for a median of 2 cycles. 281 patients received post-ASCT maintenance including 107 (38%) len, 53 (19%) bor-len, 91 (32%) dara-len, 14 (5%) dara, 16 (6%) other. The median follow-up time for all patients was 26 months (mo) (17-39). The ORR and MRD- rate (after induction) for patients who received once-weekly bor was 94% and 24%, compared to 94% and 27% for patients who received 2x weekly bor (p=0.85, p=0.93). Patients that received 2x weekly bor were not more likely to have RI (p=0.16).

The best ORR to induction for patients who underwent ASCT was 98% with 247 (79%) achieving ≥VGPR, and 82/231 (36%) achieving MRD- in the bone marrow. 96% of ASCT patients received melphalan 200mg/m2 and the ORR at day 100 was 97% with 63% (174 out of 276 evaluated) achieving MRD-. At 1-year post-ASCT, 72% (93/109) were MRD-. The median PFS was not reached (NR) (**Figure 1A**). For patients who underwent ASCT, the PFS at 24 mo for patients who did not have HR FISH was 96% (90-100%) compared to 92% (86-98%) for patients with HR FISH and 83% (76-91%) for patients with ultra-HR FISH (p=0.039) (**Figure 1B**). The PFS at 24 mo for patients with RI who underwent ASCT was 94% (86-100%) compared to 90% (86-94%) for those without RI, p=0.57. The PFS at 24 mo for patients who received post-ASCT len maintenance was 93% vs. 90% for patients who received dual agent maintenance (dara-len or bor-len) (p=0.25), although patients who got dual agent maintenance were more likely to have HR FISH than patients who received len maintenance (p<0.001). For patients with HR FISH, PFS at 24 mo with dara-len maintenance was 90.4% compared to 86.5% for bor-len maintenance (p=0.60). The PFS at 24 mo for patients that received post-ASCT consolidation was 91% compared to 85% for those that did not (p=0.53); patients who got post-ASCT consolidation were more likely to have HR FISH (p=0.07) and were more likely to be MRD+ (OR=2.99, p=0.091). For patients that underwent ASCT, the 3 yr PFS rate was 85% and the 3 yrs OS rate was 96% (**Figure 1A**) and those that achieved MRD- at anytime had a median PFS that was NR compared to 53 mo (26-NA) for patients that did not achieve MRD- (p<0.001) (**Figure 1C**). 55 patients had functional HR (FHR) MM (relapse within 18 mo of front-line

therapy) and the median PFS for FHR patients who underwent ASCT was 15 mo (11-NA), while median PFS was NR for patients without FHR MM ($p<0.001$).

The best ORR for patients who did not undergo ASCT was 87% and 30 out of 85 (35%) evaluated achieved MRD- at any time. The median PFS was 57 mo (52-NA) (**Figure 1D**) for patients who did not undergo ASCT. The PFS at 24 mo of patients with RI who did not undergo ASCT was 53% (28-100%) compared to 64% (55-75%) for those without RI, $p=0.42$. For patients that did not undergo ASCT, the 3 yrs PFS rate is 60% and the 3 yr OS rate is 85% (**Figure 1D**).

79 patients relapsed after 1st line DVRd. The most common 2nd line therapies were clinical trial (n=3), dara-carfilzomib (K)-d (n=7), dara-pomalidomide(P)-d (n=7), KPd (n=15), and other (n=41). The median follow-up time from 2nd line therapy was 10 mo, the best ORR to 2nd line therapy was 76%, and the median PFS with 2nd line therapy was 18 mo (7-NA) (**Figure 1E**). The most common second-line therapies for patients with FHR were DKD (n=5), KPD (n=11), other (n=33). For patients with FHR disease, at a median follow-up of 10 mo, the ORR was 61.8%, and the median PFS was 18 mo with second-line therapy.

In this RW analysis, the survival outcomes of NDMM patients treated with DVRd and ASCT were comparable to that reported in the PERSEUS trial. In PERSEUS, the PFS rate at 3 years was around 95% and the OS rate was around 96% (1) whereas in our RW study the 3 year PFS and OS rates were 85% and 96%, respectively. Efficacy was comparable between PERSEUS and our study as the ORR to DVRd induction in PERSEUS was 96.6% (95.2% ≥VGPR) (1) and was 98% (79% ≥VGPR) in our study. The PFS rate at 24 mo for patients with high-risk FISH (including 1q abnormalities) was similar between our study (92%) and PERSEUS (around 90%) (4). The majority of the patients in our study got once weekly bor (86%) and there were no differences in ORR or MRD- rates after induction in patients treated with DVRd and ASCT who got once vs. twice weekly bor. This is in line with clinical practice in the United States where the majority of physicians use once weekly bor (5, 6). Post-ASCT consolidation was only used in 13% (n=42) of patients in our study yet PFS at 3 years were similar to PERSEUS.

It is difficult to draw conclusions about the benefit of dual agent maintenance in our study as those who received dual-agent maintenance were more likely to have HR cytogenetics. Nonetheless, amongst HR FISH patients, the PFS was similar whether patients received dara-len or bor-len maintenance which speaks to the previously reported efficacy of these maintenance regimens in PERSEUS (dara-len) and in other RW studies with bor-len (1, 7). The PERSEUS study was not designed to evaluate the benefit of adding dara to len in the maintenance setting. The AURIGA trial demonstrated a PFS and MRD- benefit for dara-len compared to len maintenance albeit all patients were dara naïve in this trial (8). The ongoing SWOG1803 study (NCT04071457) will be able to evaluate the benefit of adding dara to len in the maintenance setting in dara-exposed patients.

32% (n=149) of patients in our study did not undergo ASCT and their 3 yrs PFS rate was 60% and 3 yr OS rate was 85%. These survival outcomes are comparable albeit PFS was lower compared to patients treated with DVRd in the CEPHEUS trial (3 yrs PFS about 80% and 3 yr OS 90%) that did not undergo ASCT (9).

Limitations of our study include its retrospective design, the relatively short follow-up, and the heterogenous patient population. Although there was heterogeneity in institutional practices for dosing of DVRd and use of consolidation and dual agent maintenance, this analysis is reflective of the variability seen in RW practice patterns. While long-term PFS modeling from the PERSEUS trial predicts a median PFS of 17 years for patients treated with the PERSEUS regimen (10), RW data will be important to evaluate how PFS in the RW compares to PERSEUS especially if consolidation and post-ASCT maintenance strategies differ from those used in PERSEUS. The results of this RW study support the efficacy of induction with DVRd +/- ASCT in patients with NDMM.

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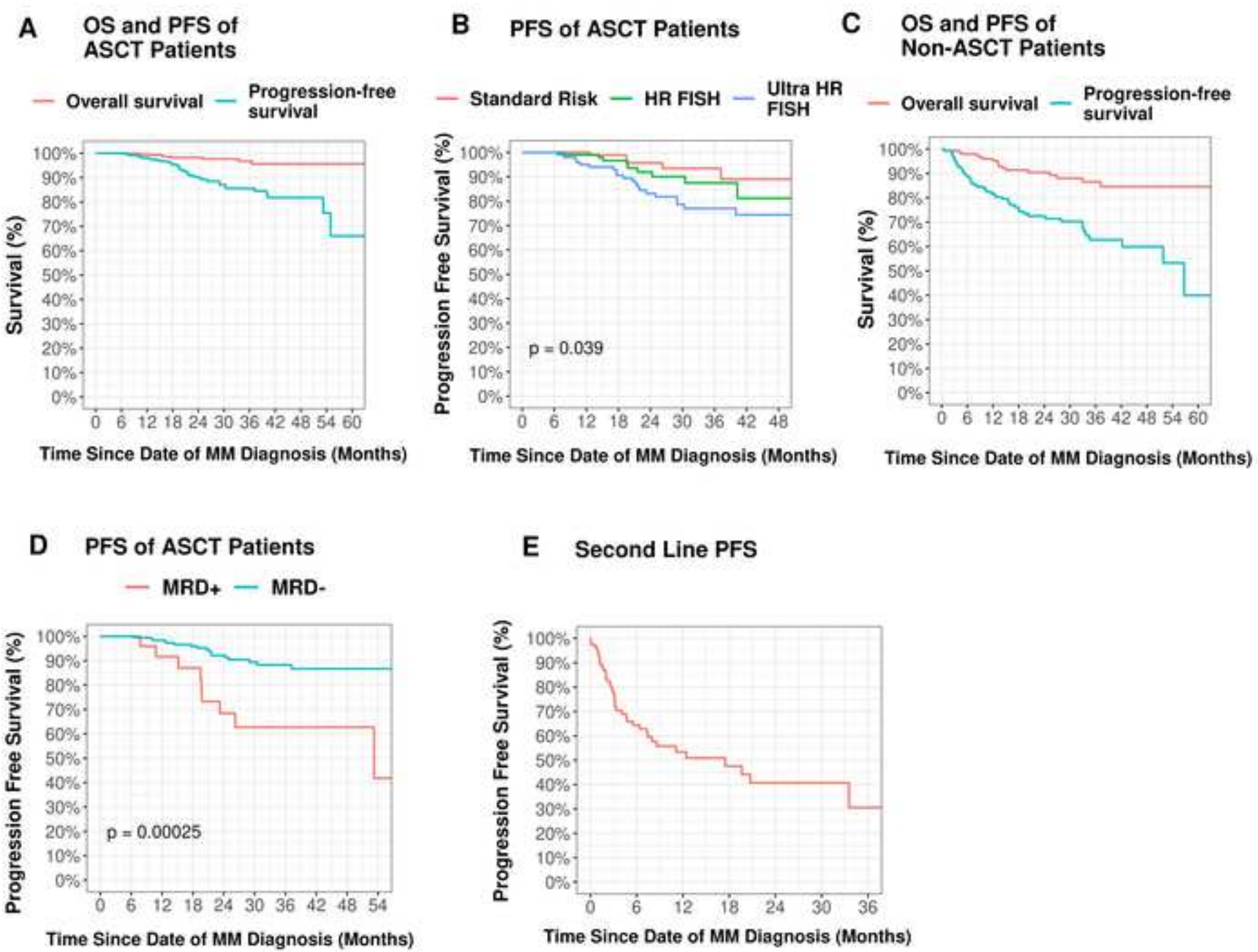
Figure Legend

Figure 1. Survival Outcomes

(A) PFS and OS of patients treated with DVRd who underwent ASCT. (B) PFS based on standard risk vs. high-risk disease. (C) PFS of DVRd–treated patients who underwent ASCT based on MRD- status at anytime. (D) PFS and OS of patients treated with DVRd who did not undergo ASCT. (E) PFS of patients who progressed after front-line DVRd and were treated with second-line therapy.



Supplemental Table 1. Patient Characteristics (N=464)	
Age, Median (range)	64.0 (26.0, 86.0)
Gender, n (%)	
Male	278 (59.9%)
Female	186 (40.1%)
Race, n (%)	
White	406 (87.7%)
Black	23 (5.0%)
Ethnicity, n (%)	
Hispanic	15 (3.2%)
Not Hispanic or Latino	438 (94.4%)
Not reported	11 (2.4%)
Myeloma Isotype, n (%)	
IgG Kappa	177 (38.1%)
IgG Lambda	77 (16.6%)
IgA Kappa	69 (14.9%)
IgA Lambda	42 (9.1%)
Kappa Light Chain	59 (12.7%)
Lambda Light Chain	21 (4.5%)
Non-Secretory	8 (1.7%)
Other	11 (2.4%)
ISS Stage, n (%)	
I	92 (19.8%)
II	151 (32.5%)
III	114 (24.6%)
N/A	107 (23.1%)
R-ISS Stage, n (%)	
I	98 (21.1%)
II	80 (17.2%)

III	205 (44.2%)
N/A	81 (17.5%)
Risk Stratification, n (%)	
Standard	182 (40.2%)
High	106 (23.4%)
Ultra High Risk	165 (36.4%)
FISH abnormalities, n (%)	
t(11;14)	66 (15.2%)
Del17p	80 (18.4%)
t(4;14)	55 (12.7%)
t(14;16)	19 (4.4%)
t(14;20)	8 (1.8%)
1q gain or amplification	193 (44.5%)
Deletion 1p	13 (3.0%)
Renal Insufficiency* at Diagnosis, n (%)	
No	417 (89.9%)
Yes	47 (10.1%)
Extramedullary Disease, n (%)	
No	384 (82.8%)
Yes	80 (17.2%)
Underwent Autologous Transplant, n%)	
No	149 (32.1%)
Yes	315 (67.9%)
*Renal insufficiency defined as creatinine >2 mg/dL and/or creatinine clearance <40 mL/min	