Comparative Effectiveness of Lenalidomide/Dexamethasone-Based Triplet Regimens for Treatment of Relapsed and/or Refractory Multiple Myeloma in the United States

Larysa Sanchez[1]; Ajai Chari[1]; Mu Cheng[2]; Dasha Cherepanov[3]; Maral DerSarkissian[2]; Dawn Marie Stull[3]; Fei Huang[3]; Annalise Hilts[2]; Justin Chun[2]; Mei Sheng Duh[2]; Sikander Ailawadhi[4]

[1] Icahn School of Medicine at Mount Sinai. New York, NY; [2] Analysis Group, Inc., Boston, MA; [3] Takeda Development Center Americas, Inc., Lexington, MA; [4] Mayo Clinic, Jacksonville, FL

Background and Study Objective

- The introduction of proteasome inhibitors (PI; e.g., bortezomib [V], carfilzomib [K], Ixazomib [I]) and monoclonal antibodies (MAB; e.g., elotuzumab [E], daratumumab [D]) have changed the treatment paradigm for the clinical management of relapsed/refractory multiple myeloma (RRMM)[1-3]
- While there is abundant clinical trial evidence to support the increased efficacy of PI- or MAB-triplet combinations with lenalidomide and dexamethasone (Rd) compared to Rd alone among the RRMM population[4-7], data on how these triplets compare to each other in real-world settings are limited
- The present study was conducted to assess the relative effectiveness of IRd, KRd, VRd, ERd, and DRd across treatment outcomes among RRMM patients, primarily treated in community oncology clinic setting, in the United States (US) with respect to duration of therapy (DOT), progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS)

Methods

Study Design and Data Source

- Retrospective longitudinal study using electronic health record (EHR) data from Flatiron Health Database spanning January 1, 2014 to September 30, 2020
- Patients ≥18 years of age with multiple myeloma (MM) initiating IRd, KRd, VRd, ERd, or DRd in line of therapy (LOT) ≥2 (index LOT) with ≥2 clinical encounters were eligible; multiple LOTs per patient were included
  - LOTs were identified with a MM LOT algorithm used in previous EHR database studies[8-10]
  - Additional rules applied to ensure complete data availability were implemented to ensure correct identification of LOTs
- Index date: initiation of Rd-backbone triplet therapy in LOT ≥2 on or after January 1, 2014
- Baseline period: up-to-6-month period before the index date
- Observation period: from the index date to the earliest of end of clinical activity, death, or end of data availability

Outcomes

- DOT: time from initiation of the index LOT until the earliest of discontinuation of the last drug in the regimen plus a run-out period (30 days for infused/injected drugs; days' supply for orally administered drugs) or death
- TTNT: time from initiation of the index LOT until the earliest of start of the subsequent LOT, end of data availability, or death
- PFS: time from initiation of the index LOT until the earliest of disease progression or death
- OS: time from initiation of index LOT until the date of death

Statistical Analysis

- Kaplan-Meier (KM) methodology and multivariable Cox proportional hazards models were used to describe and compare DOT, TTNT, PFS, and OS across regimens
- Models were adjusted for baseline patient characteristics, including age, Eastern Cooperative Oncology Group (ECOG) score, prior exposure to a PI/IMID/MAB, prior SCT, refractory status to lenalidomide/PIs/IMIDs/MABs, refractory status to last therapy, any CRAB symptoms, cytogenetics, International Staging System (ISS) stage, progression event in LOT prior to the index date, time from MM diagnosis to index date, calendar year of index date, and line of therapy
- Analyses were conducted in all LOT ≥2 and separately in LOT2, LOT3 and LOT ≥4

Results

Study Population

- N = 1,185 patients contributing 1,332 LOTs were included
- Median age was 71 years across regimens, most (63.5%) regimens were in LOT2, and the majority of patients (89.6%) were treated in community oncology clinic settings (**Table 1**)
- Median follow-up was 18 months

Baseline Characteristics

Table 1. Baseline Demographic and Treatment History

	Overall (N = 1,332)	IRd (N = 245)	KRd (N = 222)	VRd (N = 568)	DRd (N = 214)	ERd (N = 83)
Time from MM diagnosis to index date, mean ± SD	**26.7 ± 20.7**	**31.0 ± 22.3**	**25.9 ± 17.5**	**21.9 ± 19.3**	**32.0 ± 22.0**	**34.6 ± 20.9**
Age at treatment initiation, years, n (%)						
18-64	**407 (30.6)**	**77 (31.4)**	**97 (43.7)**	**135 (23.8)**	**66 (30.8)**	**32 (38.6)**
65-74	400 (30.0)	73 (29.8)	71 (32.0)	161 (28.3)	71 (33.2)	24 (28.9)
≥75	**525 (39.4)**	**95 (38.8)**	**54 (24.3)**	**272 (47.9)**	**77 (36.0)**	**27 (32.5)**
Male, n (%)	716 (53.8)	130 (53.1)	121 (54.5)	300 (52.8)	120 (56.1)	45 (54.2)
Community practice, n (%)	**1,193 (89.6)**	**208 (84.9)**	**206 (92.8)**	**518 (91.2)**	**187 (87.4)**	**74 (89.2)**
ISS stage at diagnosis, n (%)						
I	290 (21.8)	54 (22.0)	48 (21.6)	115 (20.2)	50 (23.4)	23 (27.7)
II	231 (17.3)	46 (18.8)	38 (17.1)	90 (15.8)	42 (19.6)	15 (18.1)
III	266 (20.0)	52 (21.2)	47 (21.2)	102 (18.0)	46 (21.5)	19 (22.9)
Unknown	**545 (40.9)**	**93 (38.0)**	**89 (40.1)**	**261 (46.0)**	**76 (35.5)**	**26 (31.3)**
Cytogenetics at diagnosis, n (%)						
High risk	**180 (13.5)**	**36 (14.7)**	**41 (18.5)**	**58 (10.2)**	**32 (15.0)**	**13 (15.7)**
Standard risk	985 (73.9)	184 (75.1)	155 (69.8)	420 (73.9)	163 (76.2)	63 (75.9)
Unknown	**167 (12.5)**	**25 (10.2)**	**26 (11.7)**	**90 (15.8)**	**19 (8.9)**	**7 (8.4)**
LOT number, n (%)						
2	**846 (63.5)**	**149 (60.8)**	**119 (53.6)**	**433 (76.2)**	**107 (50.0)**	**38 (45.8)**
3	**301 (22.6)**	**57 (23.3)**	**65 (29.3)**	**98 (17.3)**	**55 (25.7)**	**26 (31.3)**
≥4	**185 (13.9)**	**39 (15.9)**	**38 (17.1)**	**37 (6.5)**	**52 (24.3)**	**19 (22.9)**
ECOG PS, n (%)						
0	331 (24.8)	77 (31.4)	54 (24.3)	128 (22.5)	52 (24.3)	20 (24.1)
1	**455 (34.2)**	**68 (27.8)**	**89 (40.1)**	**170 (29.9)**	**86 (40.2)**	**42 (50.6)**
2	140 (10.5)	22 (9.0)	20 (9.0)	67 (11.8)	22 (10.3)	9 (10.8)
3	32 (2.4)	6 (2.4)	2 (0.9)	19 (3.3)	4 (1.9)	1 (1.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	**374 (28.1)**	**72 (29.4)**	**57 (25.7)**	**184 (32.4)**	**50 (23.4)**	**11 (13.3)**
Prior SCT, n (%)	**365 (27.4)**	**84 (34.3)**	**81 (36.5)**	**86 (15.1)**	**85 (39.7)**	**29 (34.9)**
Refractory to drug class, n (%)						
IMIDs	**117 (8.8)**	**35 (14.3)**	**14 (6.3)**	**37 (6.5)**	**22 (10.3)**	**9 (10.8)**
PIs	**574 (43.1)**	**145 (59.2)**	**146 (65.8)**	**50 (8.8)**	**176 (82.2)**	**57 (68.7)**
MABs	**50 (3.8)**	**15 (6.1)**	**11 (5.0)**	**4 (0.7)**	**11 (5.1)**	**9 (10.8)**
Refractory to last therapy, n (%)	1,035 (77.7)	189 (77.1)	173 (77.9)	454 (79.9)	154 (72.0)	65 (78.3)
Any CRAB symptoms, n (%)	**769 (57.7)**	**124 (50.6)**	**130 (58.6)**	**357 (62.9)**	**120 (56.1)**	**38 (45.8)**

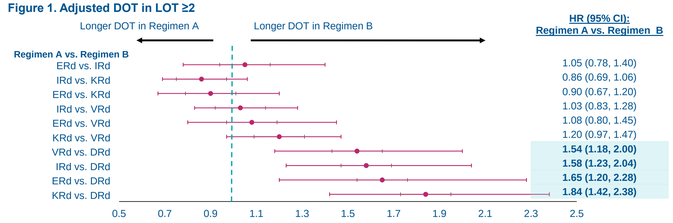
Note: [1] Bolded and highlighted results represent p<0.05.

Results – Overall

DOT

- After adjustment for baseline covariates, median DOT was 15.4 months for DRd, 9.7 months for IRd and VRd, 9.0 months for ERd, and 7.9 months for KRd
- DRd was associated with longer DOT compared to all triplets (**Figure 1**)
- No statistical differences were found for other comparisons

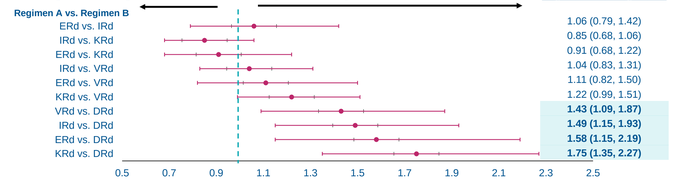
Figure 1. Adjusted DOT in LOT ≥2



TTNT

- Adjusted median TTNT was 16.9 months for DRd, and 11.2, 10.8, 10.2, and 9.1 months for VRd, IRd, ERd, and KRd, respectively
- TTNT was longer for DRd relative to all triplets (**Figure 2**)
- No statistical differences were found for other comparisons

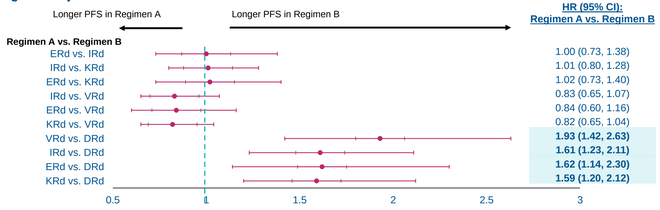
Figure 2. Adjusted TTNT in LOT ≥2



PFS

- After adjustment for baseline covariates, median PFS was longer for DRd (19.0 months) than for ERd (10.4 months), IRd (10.1 months), KRd (9.3 months) and VRd (8.8 months)
- DRd was associated with prolonged PFS in comparison to all triplets (**Figure 3**)
- No statistical differences were found for other comparisons

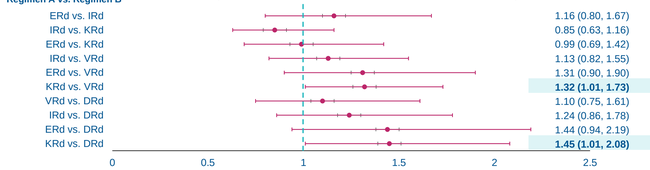
Figure 3. Adjusted PFS in LOT ≥2



OS

- Median OS after adjustment for baseline covariates was longer for DRd (29.4 months) than for ERd (25.5 months), VRd (25.3 months), IRd (24.9 months) and KRd (24.1 months)
- KRd was associated with significantly shorter OS compared with DRd and VRd across all LOTs (**Figure 4**)
- No statistical differences were found for other comparisons

Figure 4. Adjusted OS in LOT ≥2



Results – Stratified Analyses

All Outcomes

- Results of stratified analyses by LOT are presented in **Table 2**
- Stratified results in LOT2 were largely consistent with the overall cohort, where DRd was associated with longer DOT and TTNT compared to all other regimens, as well as longer PFS compared to ERd, IRd, and VRd, and longer OS compared to KRd
- In LOT3, DRd demonstrated longer DOT compared KRd. KRd was associated with shorter OS compared to VRd and IRd.
- In LOT ≥4, DRd was associated with prolonged DOT compared to IRd and VRd
- No statistical differences were found for other LOT-stratified comparisons of outcomes. Due to small sample size, results for ERd in LOT3 (N=26) and LOT ≥4 (N=19) were not considered.

Table 2. Multivariate Analysis of Outcomes by LOT

	DOT HR (95% CI)	TTNT HR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
LOT2 (N=846)				
KRd (N = 119) vs. DRd (N = 107)	**2.00 (1.39, 2.89)**	**2.05 (1.40, 3.00)**	1.47 (1.00, 2.17)	**1.77 (1.00, 3.11)**
ERd (N = 38) vs. DRd (N = 107)	**2.15 (1.33, 3.47)**	**2.07 (1.25, 3.43)**	**2.12 (1.23, 3.68)**	1.52 (0.77, 2.99)
IRd (N = 149) vs. DRd (N = 107)	**1.72 (1.20, 2.48)**	**1.71 (1.17, 2.51)**	**1.71 (1.19, 2.45)**	1.71 (0.97, 3.01)
VRd (N = 433) vs. DRd (N = 107)	**1.56 (1.04, 2.33)**	**1.57 (1.02, 2.41)**	**1.99 (1.27, 3.14)**	1.21 (0.65, 2.25)
KRd (N = 119) vs. VRd (N = 433)	1.29 (0.96, 1.74)	1.32 (0.96, 1.80)	0.74 (0.51, 1.08)	1.46 (0.96, 2.22)
ERd (N = 38) vs. VRd (N = 433)	1.38 (0.87, 2.19)	1.33 (0.83, 2.14)	1.06 (0.61, 1.85)	1.26 (0.70, 2.26)
IRd (N = 149) vs. VRd (N = 433)	1.11 (0.82, 1.50)	1.10 (0.80, 1.51)	0.86 (0.59, 1.23)	1.41 (0.91, 2.19)
ERd (N = 38) vs. KRd (N = 119)	1.07 (0.70, 1.64)	1.01 (0.65, 1.57)	1.44 (0.86, 2.42)	0.86 (0.50, 1.49)
IRd (N = 149) vs. KRd (N = 119)	0.86 (0.65, 1.14)	0.83 (0.62, 1.12)	1.16 (0.84, 1.59)	0.97 (0.65, 1.44)
ERd (N = 38) vs. IRd (N = 149)	1.25 (0.81, 1.92)	1.21 (0.78, 1.89)	1.24 (0.75, 2.06)	0.89 (0.51, 1.54)
LOT3 (N=301); only significant results are presented				
KRd (N = 65) vs. DRd (N = 55)	**1.73 (1.09, 2.75)**	1.47 (0.92, 2.34)	1.75 (0.99, 3.09)	1.44 (0.78, 2.66)
KRd (N = 65) vs. VRd (N = 98)	1.36 (0.95, 1.96)	1.33 (0.92, 1.93)	1.02 (0.68, 1.53)	**1.73 (1.11, 2.71)**
IRd (N = 57) vs. KRd (N = 65)	0.80 (0.52, 1.22)	0.88 (0.57, 1.37)	0.74 (0.46, 1.22)	**0.39 (0.20, 0.76)**
LOT ≥4 (N=185); *only significant results are presented*				
IRd (N = 39) vs. DRd (N = 52)	**2.20 (1.11, 4.35)**	1.95 (1.00, 3.80)	1.51 (0.77, 2.96)	0.92 (0.39, 2.17)
VRd (N = 37) vs. DRd (N = 52)	**2.14 (1.08, 4.23)**	1.69 (0.84, 3.42)	1.71 (0.82, 3.58)	0.83 (0.29, 2.33)

Conclusions

- PI-containing Rd-based triplet regimens (i.e., VRd, KRd, and IRd) and ERd generally showed comparable effectiveness in real-world outcomes of US RRMM patients under routine clinical care in primarily community oncology clinic setting; results are confirmed by stratified analysis by LOT
- Consistent with prior evidence10-12, DRd was associated with statistically significantly better PFS, DOT, TTNT, and in some cases OS, compared to other Rd-based triplet regimens (i.e., KRd, DRd, IRd, and ERd)
- Data on the effectiveness of therapies in routine community oncology clinical care settings provide key supplemental evidence to clinical trials, thereby informing treatment recommendations

Limitations

- Due to the nature of real-world observational analyses, the evaluation of outcomes (e.g., progression) may not be consistent across subjects and physicians may be subject to surveillance bias
- Complexities may arise from deriving clinically-relevant data from the Flatiron EHR database, including miscoding and misclassification of diagnosis codes and incomplete data, leading to potential bias due to residual and/or unmeasured confounding
- Treatment patterns observed in this study represent those of patients treated in a community oncology setting and may differ from those observed at other clinical sites, such as academic medical centers

References

1. Jakubowiak A. *Semin Hematol.* 2012;49 Suppl 1:S16-32.
2. D'Agostino et al. *Int J Mol Sci.* 2020 Nov 1;21(21):8192.
3. Moreau. *Semin Hematol.* 2012;49 Suppl 1:S33-46.
4. Moreau et al. *N Engl J Med.* 2016;374:1621-1634.
5. Richardson et al. *Blood*. 2014;123(10):1461-1469.
6. Bahlis et al. *Leukemia.* 2020;34(7):1875-1884.
7. Dimopoulos et al. *Cancer*. 2018;124(20):4032-4043.
8. Chari et al. *Expert Rev Hematol.* 2020;13(4):421-433.
9. Berger et al. *EHA-1667*. 2021: 324313.
10. Davies et al. *Ann Hematol.* 2021;100(9):2325-2337
11. Maiese et al. *Clin Therapeutics.* 2018;40(3):480-494.
12. Dimopoulos et al. *Clin Lymphoma Myeloma Leuk.* 2018 Mar;18(3):163-173.e6.

Acknowledgements

The authors thank Mona Lisa Chanda, PhD, an employee of Analysis Group, Inc., for her medical writing support, and Steve Noga, MD, PhD and Kimberly Bogard, PharmD, BCPS, employees of Takeda Oncology, for their contributions to the conception and design of this study.

Disclosures

This study was supported by Takeda Development Center Americas, Inc. MC, MD, AH, JC and MSD are employees of Analysis Group, a consulting firm that received funding from Takeda Development Center Americas, Inc., to conduct this study. DC, DMS, and FH are employees of Takeda Development Center Americas, Inc. LS, AC, and SA have receiving consulting funds from Takeda Development Center Americas, Inc.

2022 International Myeloma Society Annual Meeting
August 25-27, 2022
Los Angeles, CA, USA

Abstract Number: 1277793