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Progression-Free Survival of Daratumumab vs. Bortezomib Triplet Combination with Lenalidomide and Dexamethasone in Transplant Ineligible Newly Diagnosed Multiple Myeloma Patients: A Chart Review Study

Lucio Gordan MD[1], Carlyn Rose Tan MD[2], Robert Vescio MD[3], Jing Christine Ye MSc, MD[4,5], Carolina Schinke MD[6], Rohan Medhekar PhD[7], Alex Z. Fu PhD[8,9], Marie-Hélène Lafeuille MA[10], Philippe Thompson-Leduc MSc[10], Vipin Khare MD[7], John Reitan PharmD[11], Gary Milkovich BS[12], Shuchita Kaila PhD[7], Faith Davies MD[13], Saad Z. Usmani MD, FACP[2]

[1]Florida Cancer Specialists & Research Institute, Gainesville, FL, USA. [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA. [3]Samuel Oschin Cancer Center, Cedars-Sinai, Los Angeles, CA, USA. [4]University of Michigan (during study), Ann Arbor, MI, USA. [5]UT MD Anderson Cancer Center (current), Houston, TX, USA. [6]University of Arkansas, Fayetteville, AR, USA. [7]Janssen Scientific Affairs, LLC, Horsham, PA, USA. [8]Janssen Scientific Affairs, LLC, Titusville, NJ, USA. [9]Georgetown University Medical Center, Washington, DC, USA. [10]Analysis Group, Inc., Montreal, QC, USA. [11]RJM Group, LLC, Chicago, IL, USA. [12]RJM Group, LLC, Washington, DC, USA. [13]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA.

INTRODUCTION

- Treatment of patients with newly diagnosed multiple myeloma (NDMM) depends on the stem cell transplant (SCT) eligibility of the patient.[1,2] Some patients such as those who are less medically fit (older and with more comorbidities) are usually transplant ineligible (TIE)[3]
- Daratumumab, lenalidomide and dexamethasone (DRd) and bortezomib, lenalidomide and dexamethasone (VRd) are currently the only preferred regimens recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for primary treatment of non-transplant patients with NDMM with Category 1 evidence[4]
- Both DRd and VRd have demonstrated superior efficacy compared with lenalidomide and dexamethasone (Rd) alone in the MAIA[5] and SWOG S0777[6] trials, respectively, but there is no head-to-head clinical trial comparing efficacy of these two regimens
- Moreover, differing patient populations in the MAIA and S0777 trials make an unadjusted comparison of outcomes challenging and biased
- The current chart review study was conducted to compare the progression-free survival (PFS) among TIE patients with NDMM receiving DRd vs VRd as first-line (1L) therapy in the real-world setting

METHODS

Study design and patient population

- A multicenter, non-interventional chart review study design was employed at nine centers across the USA
- Patients were included if they had a confirmed diagnosis of MM, were ≥65 years old at diagnosis, were considered TIE by the treating physician, and had initiated DRd or VRd as 1L treatment between January 2019 and September 2021
- Patients who had received a SCT prior to date of DRd/VRd initiation (index date), had participated in an interventional clinical trial for MM, had an invasive malignancy other than MM, or had received treatment for >30 days before index date (except corticosteroids) were excluded
- All eligible DRd recipients, and a random sample of eligible VRd recipients (to match the number of patients in the DRd cohort) were included
- Patients were followed from the index date until the last date of clinical activity or death, and no later than 25 January 2023 (Figure 1)

Data source and variables

- Data from patient charts were abstracted in a standardized electronic chart review form (eCRF) by research staff at the sites and data collection occurred between 16 August 2021 and 25 January 2023
- Baseline patient and clinical characteristics were assessed
- Duration of treatment was defined as the time between the index date and discontinuation of all agents in the regimen (including maintenance therapy with lenalidomide)

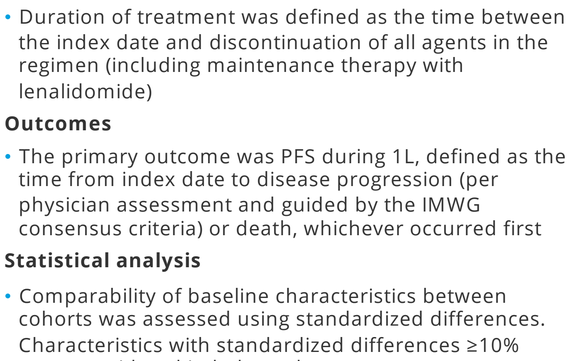
Outcomes

- The primary outcome was PFS during 1L, defined as the time from index date to disease progression (per physician assessment and guided by the IMWG consensus criteria) or death, whichever occurred first

Statistical analysis

- Comparability of baseline characteristics between cohorts was assessed using standardized differences. Characteristics with standardized differences ≥10% were considered imbalanced
- The inverse probability of treatment weighting (IPTW) method was used to balance differences in baseline characteristics between cohorts
  - The weight assigned to each patient was derived from a propensity score calculated using multivariate logistic regression, where the dependent variable was cohort assignment (DRd or VRd), and baseline characteristics were used as independent variables to predict cohort assignment
- PFS for the weighted DRd and VRd cohorts was reported using IPTW-weighted Kaplan-Meier (KM) curves
  - Patients with no indication of disease progression or death were censored at the date of initiation of next line of therapy or last clinical activity recorded, whichever occurred first
- A doubly-robust weighted Cox regression model was used to compare PFS between cohorts, which adjusted for patient characteristics that remained imbalanced after weighting. Results were reported as an adjusted hazard ratio (HR) with 95% CI and p-value

FIGURE 1. TAURUS study design



1L = first line of therapy; DRd = daratumumab plus lenalidomide and dexamethasone; MM = multiple myeloma; VRd = bortezomib plus lenalidomide and dexamethasone.

MULTIPLE MYELOMA

RESULTS

Sample description

- Charts of 99 DRd and 79 VRd patients were extracted
- Prior to weighting, some differences in the baseline characteristics between the two cohorts were observed:
  - In the DRd cohort, patients were slightly older, more patients had hypertension and solid tumors, and more frail patients were included. The mean BMI and mean modified Charlson Comorbidity Index (CCI) score were lower in this cohort
  - The VRd cohort had a higher proportion of females, African Americans, 1q21 amplification/gain, and high risk-patients. The proportion of patients with diabetes, chronic obstructive pulmonary disease, rheumatological disease and cerebrovascular disease was higher in this cohort
- After weighting (DRd weighted n=91, VRd weighted n=87), these characteristics were well balanced between cohorts (Table 1 and Table 2):
  - Small differences were observed in year of index date and International Staging System (ISS) staging (Table 1) which were added as regressors to the Cox model
- The median length of follow-up in the DRd and VRd cohorts was 18.3 (range: 1.9-36.9) and 20.1 (range: 2.0-39.4) months, respectively
- Mean (standard deviation) duration of treatment in the DRd and VRd cohorts was 13.9 (7.6) and 7.3 (5.6) months, respectively

TABLE 1: Key baseline patient and clinical characteristics

	Weighted cohorts[1]		
	DRd	VRd	Std. Diff.
	n=91	n=87	
Age, mean ± SD [median]	76.2 ± 5.8 [76.0]	75.9 ± 6.1 [75.0]	4.5
Age categories, n (%)			
65 to <70 years	15 (16.6)	13 (15.5)	3.2
70 to <75 years	21 (22.9)	21 (24.1)	2.9
≥75 years	55 (60.5)	53 (60.5)	0.1
Height (cm), mean ± SD [median]	167.4 ± 9.3 [167.4]	166.6 ± 10.6 [166.0]	7.5
Weight (kg), mean ± SD [median]	79.5 ± 18.3 [78.0]	80.5 ± 23.6 [74.7]	4.7
BMI, mean ± SD [median]	28.3 ± 6.1 [27.4]	28.8 ± 7.1 [26.1]	6.6
Gender, n (%)			
Female	47 (51.1)	45 (52.0)	1.8
Race, n (%)			
White	48 (53.1)	46 (53.0)	0.2
Black or African American	13 (14.2)	13 (14.8)	1.7
Other[2] or unknown	30 (32.7)	28 (32.2)	1.1
ECOG performance status, n (%)			
0	29 (32.0)	28 (31.7)	0.5
1 or 2	53 (57.7)	50 (58.0)	0.7
3 or 4	2 (2.7)	3 (3.7)	5.6
Unknown	7 (7.7)	6 (6.6)	4.2
ISS stage, n (%)			
I	22 (24.5)	23 (27.0)	5.7
II	27 (29.9)	21 (24.4)	12.5*
III	16 (17.7)	15 (17.2)	1.4
Unknown	25 (27.9)	27 (31.5)	7.9
Cytogenetic risk, n (%)			
High risk (del(17p), t(14;16), t(4;14) abnormality)	13 (14.4)	15 (17.2)	7.8
Standard risk	54 (58.9)	47 (54.2)	9.4
Unknown	24 (26.7)	25 (28.6)	4.1
1q21 amplification or gain, n (%)			
Yes	23 (25.5)	24 (27.7)	4.9
No	58 (63.4)	52 (60.4)	6.3
Unknown	10 (11.0)	10 (11.9)	2.8
Time from MM diagnosis to index date (months), mean ± SD [median]	3.3 ± 7.8 [0.9]	3.3 ± 7.5 [1.0]	0.7
Year of index date, n (%)			
2019	14 (15.7)	32 (36.9)	49.5*
2020	33 (35.7)	36 (41.1)	11.0*
2021	44 (48.6)	19 (22.1)	57.7*

*Standardized difference ≥10%. BMI = body mass index; cm = centimeter; DRd = daratumumab plus lenalidomide and dexamethasone; ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; kg = kilogram; MM = multiple myeloma; SD = standard deviation; Std. Diff. = standardized difference; VRd = bortezomib plus lenalidomide and dexamethasone. [1] Weights were estimated using a multivariable logistic regression model with the following baseline covariates: age categories, female, race, height, BMI, ECOG, ISS, cytogenetic risk, presence of 1q21 amplification or gain, site, time from MM diagnosis to index date, frailty, CCI score and selected comorbidities: hypertension, diabetes, peripheral neuropathy, chronic obstructive pulmonary disease, renal disease, congestive heart failure, solid tumor, rheumatological disease, cerebrovascular disease, peptic ulcer disease, and myocardial infarction. [2] Includes Asian, Hispanic or Latino, Native Hawaiian or other Pacific Islander, mixed, American Indian and Alaska Native.

TABLE 2. Key comorbidities and frailty score

	Weighted cohorts[1]		
	DRd	VRd	Std. Diff.
	n=91	n=87	
Modified CCI, mean ± SD [median]	1.2 ± 1.5 [1.0]	1.3 ± 1.3 [1.0]	5.1
Component comorbidities, n (%)	73 (79.6)	70 (80.6)	2.5
Hypertension	63 (68.9)	57 (65.2)	7.7
Moderate or severe renal disease	24 (25.9)	24 (27.6)	3.8
Coronary heart disease	18 (20.0)	15 (17.3)	7.0
Diabetes mellitus	19 (20.9)	20 (23.6)	6.3
Peripheral neuropathy	11 (12.0)	10 (12.0)	0.1
Chronic obstructive pulmonary disease	10 (11.1)	10 (11.9)	2.6
Congestive heart failure	6 (6.8)	6 (7.2)	1.4
Solid tumor	5 (5.4)	4 (4.7)	3.3
Peripheral vascular disease	5 (5.3)	3 (3.8)	7.0
Myocardial infarction	4 (4.8)	4 (4.7)	0.6
Rheumatological disease	5 (5.4)	6 (6.6)	4.8
Cerebrovascular disease	3 (3.3)	3 (3.6)	1.6
Mild liver disease	1 (0.9)	1 (1.5)	5.7
Peptic ulcer disease	2 (1.8)	2 (2.4)	4.2
Dementia	0 (0.0)	1 (0.9)	13.2*
HIV/AIDS	0 (0.0)	0 (0.0)	0.0
Hemiplegia or paraplegia	0 (0.0)	0 (0.0)	0.0
Frailty score[2] ≥2 , n (%)	55 (60.3)	53 (60.6)	0.6

*Standardized difference ≥10%. DRd = daratumumab plus lenalidomide and dexamethasone; CCI = Charlson Comorbidity Index; SD = standard deviation; Std. Diff. = standardized difference; VRd = bortezomib plus lenalidomide and dexamethasone. [1] Weights were estimated using a multivariable logistic regression model with the following baseline covariates: age categories, female, race, height, BMI, ECOG, ISS, cytogenetic risk, presence of 1q21 amplification or gain, site, time from MM diagnosis to index date, frailty, CCI score and selected comorbidities: hypertension, diabetes, peripheral neuropathy, chronic obstructive pulmonary disease, renal disease, congestive heart failure, solid tumor, rheumatological disease, cerebrovascular disease, peptic ulcer disease, and myocardial infarction. [2] Calculation of frailty is based on three components: Age (≤75 years = 0 point, 76-80 years = 1 point, >80 years = 2 points), CCI (≤1 = 0 point, >1 = 1 point), and ECOG performance status (0 = 0 point, 1 = 1 point, ≥2 = 2 points)

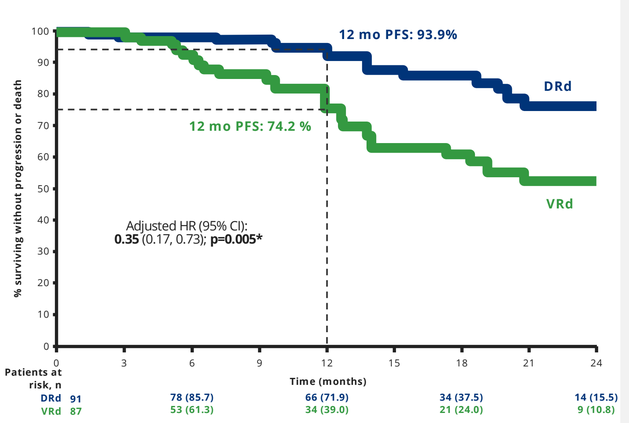
Comparison of progression-free survival

- At data cut-off, 13 DRd (14.5%) and 24 VRd (28.2%) patients experienced disease progression or death
- At 12 months, the KM rate of patients without progression or death was 93.9% among DRd patients and 74.2% among VRd patients (log-rank test: p=0.006; Figure 2)
- The doubly-robust IPTW-weighted analysis showed that patients treated with 1L DRd had a 65% lower risk of disease progression or death compared with 1L VRd (adjusted hazard ratio=0.35, 95% CI: 0.17, 0.73, p=0.005; Figure 2)

Limitations

- Data analyzed were limited to the information collected in medical charts available at the centers, which do not constitute a closed system. Physician notes often capture care that is received outside of the centers; however, some services received outside of the centers may not be fully captured
- It is possible that there were some differences in the level of missing data between centers
- Results could be subject to residual confounding due to unmeasured confounders which were not captured as part of the eCRF
- Patients were required to be ≥65 years old and TIE at initial MM diagnosis. Therefore, findings of this study may not translate to other populations

FIGURE 2. Adjusted PFS among TIE NDMM patients initiated on 1L DRd or VRd



*Indicates statistical significance at p<0.05 CI = confidence interval; DRd = daratumumab plus lenalidomide and dexamethasone; HR = hazard ratio; VRd = bortezomib plus lenalidomide and dexamethasone [1] Weights were estimated using a multivariable logistic regression model with the following baseline covariates: age categories, female, race, height, BMI, ECOG, ISS, cytogenetic risk, presence of 1q21 amplification or gain, site, time from MM diagnosis to index date, frailty, CCI score and selected comorbidities: hypertension, diabetes, peripheral neuropathy, chronic obstructive pulmonary disease, renal disease, congestive heart failure, solid tumor, rheumatological disease, cerebrovascular disease, peptic ulcer disease, and myocardial infarction. [2] In addition to the IPTW adjustment, the doubly robust Cox model included year of index date and ISS stage.

KEY TAKEAWAY

DRd was associated with a significantly lower risk of disease progression or death compared with VRd as 1L treatment for patients with TIE NDMM in a real-world setting

CONCLUSIONS

Based on this retrospective chart review, DRd was associated with a significantly lower risk of disease progression or death compared with VRd as 1L treatment for patients with TIE NDMM

As these are the only guideline-recommended preferred regimens in this population, results from this TAURUS chart review study could help inform the selection of optimal 1L treatment for TIE NDMM patients in the absence of head-to-head clinical trials

These findings add to the growing body of evidence demonstrating superiority of DRd vs VRd as 1L treatment for patients with TIE NDMM

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DISCLOSURES

LG is an employee of Florida Cancer Specialists; served as a consultant or advisor for Illumina, IntegraConnect, Tolmar, and Janssen Oncology; held a leadership role at Florida Cancer Specialists; holds stock or other ownership interests at Florida Cancer Specialists and Research Institute and American Oncology Network; and received honoraria from Ameris Pharma. **CRT** received research funding from Janssen and Takeda and served on an advisory board for Janssen. **RV** served on a Speaker's Bureau for Amgen, Bristol Myers Squibb, Janssen, Alnylam, and Karyopharm. **JCY** served on an ad board, as a consultant, and/or received research funds from Janssen, Regeneron, Pfizer, AbbVie, Bristol Myers Squibb, Novartis, Genmab, Mingsight, and Eli Lilly. **CS** served on a consulting and advisory panel for Janssen. **RM, AZF, VK** and **SK** are employees of Janssen Scientific Affairs, LLC, and may own stock/stock options. **M-HL** and **PT-L** are employees of Analysis Group, Inc., a consulting firm that has received research funding from Janssen for the conduct of this study. **JR** and **GM** are employees of RJM GROUP LLC., a consulting firm that has received research funding from Janssen for the conduct of this study. **FD** served on advisory boards for Sanofi, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Pfizer, Janssen, Oncopeptides, Amgen, and Takeda. **SU** served as consultant or advisor for Celgene, Amgen, Janssen Oncology, Seattle Genetics, Takeda, GlaxoSmithKline, Karyopharm Therapeutics, AbbVie, SkylineDX, Merck, Oncopeptides, Genentech, Gilead Sciences, and Bristol Myers Squibb/Celgene; served on a speakers' bureau for Takeda, Amgen, Janssen Oncology, Sanofi, and Bristol Myers Squibb/Celgene; and received research funding from Celgene and Array BioPharma.

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