REGULAR ARTICLE

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Real-world comparison of daratumumab-based regimens in relapsed/refractory multiple myeloma using health record data

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Key Points

- Among patients receiving 2L/3L therapy, dara-Vd was associated with inferior rwTTNT compared with both dara-Kd and dara-Pd.
- No regimen was associated with statistically superior rwOS.

Daratumumab (dara)-based triplet therapies are commonly used in the second-line (2L) and third-line (3L) settings in relapsed/refractory multiple myeloma (RRMM), usually in combination with dexamethasone and either bortezomib (dara-Vd), carfilzomib (dara-Kd), or pomalidomide (dara-Pd). We performed a real-world (rw) analysis to directly compare these regimens, to our knowledge, for the first time. This was an observational, retrospective cohort study using COTA's rw database of patients with MM who have initiated 2L or 3L therapy with dara-Vd, dara-Kd, or dara-Pd. rw time to next treatment (rwTTNT) and rw overall survival (rwOS) were analyzed using the Kaplan-Meier method. Comparative analyses were conducted using a trimmed inverse probability of treatment weighting method to control for potential confounders. A total of 639 patients received a dara-based regimen as either 2L or 3L therapy (dara-Vd, n = 201; dara-Kd, n = 122; and dara-Pd, n = 316). A high proportion had functional (52%) or cytogenetic (26%) high-risk disease; 49% were lenalidomide refractory. Median rwTTNT for dara-Vd was 7.6 months and was 12.9 months for dara-Kd (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.49-0.99). Similarly, median rwTTNT for dara-Vd was 6.9 months and 15.3 months for dara-Pd (HR, 0.57; 95% CI, 0.43-0.77). Median rwTTNT for dara-Pd was 15.7 months, and for dara-Kd 13.2 months (HR, 1.1; 95% CI, 0.8-1.6). No regimen was associated with superior rwOS. Among patients with RRMM receiving 2L or 3L therapy with a dara-based triplet, dara-Vd was associated with inferior rwTTNT compared with both dara-Kd and dara-Pd. dara-Vd may not be a suitable control arm for most phase 3 studies.

Introduction

Frontline "triplet" therapy with a proteasome inhibitor, immunomodulatory drug, and corticosteroid has been the standard of care for patients with newly diagnosed multiple myeloma (MM) in the United States for many years. Although this treatment strategy ushered in a new era of stepwise improvements in the MM treatment paradigm that meaningfully improved overall survival (OS), it is not curative for most patients.

Daratumumab (dara), a CD38-targeting humanized monoclonal antibody, demonstrated single-agent activity in patients with heavily pretreated MM.[1] Additionally, dara-containing triplet therapies have been studied in patients after 1 to 2 prior lines of therapy. These combinations include dexamethasone

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The online version of this article contains a data supplement.

(d)-containing triplet therapies with bortezomib (V),[2] a second-generation proteasome inhibitor carfilzomib (K),[3,4] or a third-generation immunomodulatory drug pomalidomide (P).[5-7] Each of these combinations showed improvements in progression-free survival (PFS) compared with the same backbone without dara. Although dara-Kd, dara-Pd, and dara-Vd are all approved in the United States for relapsed/refractory (RR) MM, the relative efficacy of these triplets, to our knowledge, has not previously been studied.

Cross-trial comparisons among these regimens are fraught, owing to differences in the characteristics of the patient populations, most notably the number of prior lines of therapy and the proportion of patients with lenalidomide refractoriness, both of which are associated with poorer outcomes.[8,9] Additionally, the proportion of patients who are refractory, or who have been exposed, to lenalidomide in the trials may not be consistent with the real-world (rw) prevalence among patients initiating second-line (2L) or third-line (3L) therapy. Lastly, most pivotal MM trials enroll a generally homogenous population of patients without adequate representation of minorities,[10] which may also limit generalizability of these results to these populations.

Rw data (RWD) derived from both academic and community practice settings can help to address these issues. Moreover, RWD serve as a mechanism to allow head-to-head comparisons of regimens that may never be adequately tested in clinical trial settings because of logistical, financial, or ethical reasons. In this study, we used a curated electronic health record (EHR) data set to compare rw time to next treatment (rwTTNT) and rw overall survival (rwOS) for 3 commonly used dara-based regimens in RRMM with 1 to 2 prior lines of therapy through a weighted propensity score model.

Methods

Study design

This was an observational, retrospective cohort study using COTA's rw database of curated EHR data to investigate the characteristics, treatment patterns, and outcomes of patients with MM who have initiated 2L or 3L therapy with dara-Vd, dara-Kd, or dara-Pd. Inclusion criteria were patients aged ≥18 years at the time of diagnosis, on or after 1 January 2015. Patients were excluded if the date of initiation of therapy, date of death, or date of last visit were missing, unknown, or imprecise. Patients were categorized according to the first dara-based triplet they received as a 2L or 3L therapy.

Patient demographic and clinical characteristics unique to MM were assessed, including exposure and refractoriness to prior therapies. Refractoriness to a drug or line of therapy (LOT) was defined as documented discontinuation because of any of the following: (1) progression or inadequate response, (2) an interval between the end of a given LOT and the start of the subsequent LOT within 60 days, or (3) an interval from the start of a given LOT to the end of that LOT within 60 days. A patient was considered to have relapsed disease to a regimen if the interval between the end of that LOT and the start of the subsequent was >60 days, the regimen was not discontinued because of progression or inadequate response, and the regimen was not discontinued within 60 days from initiation. For consistency and clarity, these definitions were as aligned as possible with those often used in clinical trials.

The LOT was assigned programmatically using an MM-specific algorithm, which groups treatment regimens into lines of therapy based on various parameters, including drug combinations, gaps in treatment, treatment phase, and reasons for discontinuation including documented progression. The algorithm incorporates both internal expert guidance and external clinical guidance, as previously published by Rajkumar et al.[11] The LOT algorithm accounts for "dropped" therapies (when only 1 component of the regimen is stopped) and does not advance the LOT in those cases.

The index date for the study was defined as the date of initiation of 2L or 3L therapy, and the window of assessment of baseline demographic and clinical characteristics was any time before initial diagnosis of MM until 30 days after initiation of therapy. If multiple values for baseline variables were present, the value closest to the index date was prioritized. In the rare scenario in which multiple values were present on the closest date, the worse value was prioritized. Characteristics variables, such as race, cytogenetic results, or Eastern Cooperative Oncology Group performance status, that were not tested/collected or tested/collected but reported as unknown were grouped together in the "unknown" category. Follow-up time was calculated from index to date of death or date of last visit (if no date of death was available).

Data source

This study used a Health Insurance Portability and Accountability Act–compliant rw database curated by COTA, Inc. This database comprises longitudinal data pertaining to the diagnosis, clinical management, and outcomes of patients with cancer. Data were abstracted from the EHRs of partnered health care provider sites, including both community and academic practices with a primary geographic concentration in the Eastern and Southern regions of the United States. COTA's data abstraction process uses both human abstraction and technologic methods to transform structured and unstructured data into a standardized data model. This database has formed the basis for numerous research publications.

End points

The primary end points of this study were to evaluate and compare rwTTNT and rwOS of dara-Vd, dara-Kd, and dara-Pd. rwTTNT was defined as the time from the index date until the date of initiation of a new LOT or death, and patients were censored at the date of last contact with a health care provider if an event had not occurred. rwOS was defined as the time from the index date until the date of death, and patients without a date of death were censored at the last clinically relevant date recorded in the COTA database. COTA's composite mortality variable leveraged both structured and unstructured EHR data and was supplemented by commercially available obituary data.

rwTTNT and rwOS were analyzed using the Kaplan-Meier (KM) method. KM estimates of median time to event(s) and Greenwood 95% confidence intervals (CIs) were calculated for the study population and for each subgroup. Comparative analyses were conducted and presented by 2 methods: unadjusted (without controlling for confounders) and trimmed inverse probability of treatment weighting (tIPTW) method. Propensity scores were estimated using a multivariable binomial logistic regression model to balance baseline demographic and clinical characteristics including: age at diagnosis, sex, race, practice type, Charlson

Comorbidity Index score group, Eastern Cooperative Oncology Group performance status score group, refractoriness to lenalidomide before dara triplet, refractoriness to bortezomib before dara triplet, refractoriness to dara before dara triplet, stem cell transplantation (SCT) before dara triplet, time from end of prior line to start of dara triplet line, functional risk (defined as disease recurrence or initiation of a 2L therapy ≤18 months after diagnosis), cytogenetic risk (defined as presence of any of the following cytogenetic markers: t(4;14), t(14;16), t(14;20), and/or 17p or TP53 deletion), International Staging System stage, and LOT of dara triplet of interest. Variables were considered to be balanced if the standardized mean difference was <0.2. Propensity scores were trimmed at 2.5 and 97.5 percentiles (dara-Vd vs dara-Kd and dara-Kd vs dara-Pd) and 2.5 and 87 percentiles (dara-Vd vs dara-Pd) to achieve better balance between groups. Variables that were not balanced after tIPTW by group were race (dara-Vd vs dara-Kd) and time between end of prior line and start of dara triplet line (dara-Vd vs dara-Pd). A Cox proportional-hazards model was adjusted for unbalanced variables and LOT and included a time-dependent variable to account for the receipt of SCT within the dara triplet LOT. This model was used to estimate the hazard ratios (HRs) for the outcomes. The "N" in the adjusted analysis was larger than that of original study population, because of the creation of a weighted pseudopopulation to balance relevant covariates.[12] The LOT adjusted medians were reported by estimating the KM curves from the stratified Cox proportional hazards model.

Results

A total of 639 patients were identified in the COTA database to have received a dara-based regimen as either 2L or 3L therapy (Figure 1). There were 201 patients in the dara-Vd group, 127 (63%) of whom received the regimen as 2L therapy. The dara-Pd group had 316 patients, 144 (46%) of whom received the regimen as 2L therapy. Of the 122 patients in the dara-Kd group, there was a near even split between those who received it as 2L therapy (n = 60, 49%) and those who received it as 3L therapy (n = 62, 51%).

Patient characteristics

Patient characteristics for the whole cohort and by treatment group can be found in Table 1 and in Supplemental Table S1. The median age at diagnosis was 66 years (interquartile range [IQR], 59-73). Most patients were White (69%); 14% were Black (25% dara-Kd, 12% dara-Pd, and 10% dara-Vd). More patients were treated in the community setting (65%) than in the academic setting (35%), although this was driven by the dara-Kd (74% vs 26%) and dara-Vd (89% vs 11%) groups and not the dara-Pd group (46% vs 54%). More than half of patients (52%) had functional high-risk disease (47% dara-Pd, 53% dara-Kd, and 61% dara-Vd). High-risk cytogenetic abnormalities were present in 26% (28% dara-Pd, 34% dara-Kd, and 19% dara-Vd), although many patients had unknown risk status (63%).

Prior treatment exposures and refractoriness were also investigated (Table 2). Among the whole cohort, 39% of patients were exposed but not refractory to lenalidomide, and 49% were refractory to lenalidomide before receipt of the triplet of interest; there was a comparable proportion of patients with lenalidomide-refractoriness in the dara-Vd group (46%), dara-Pd group (52%), and dara-Kd group (47%). In the dara-Vd group, 53% of patients were already refractory to bortezomib. There were 15 cases of pomalidomide refractoriness in the dara-Pd group, and there were 5 cases of carfilzomib-refractoriness in the dara-Kd group. Only 9% of patients had prior exposure to daratumumab across all groups (6% refractory), with exposures of 8%, 12%, and 8% in the dara-Pd, dara-Kd, and dara-Vd groups, respectively. Half of the study population had received a prior autologous SCT (62% of the dara-Pd group, 57% of the dara-Kd group, and 26% of the dara-Vd group).

Figure 1. Patient attrition diagram.

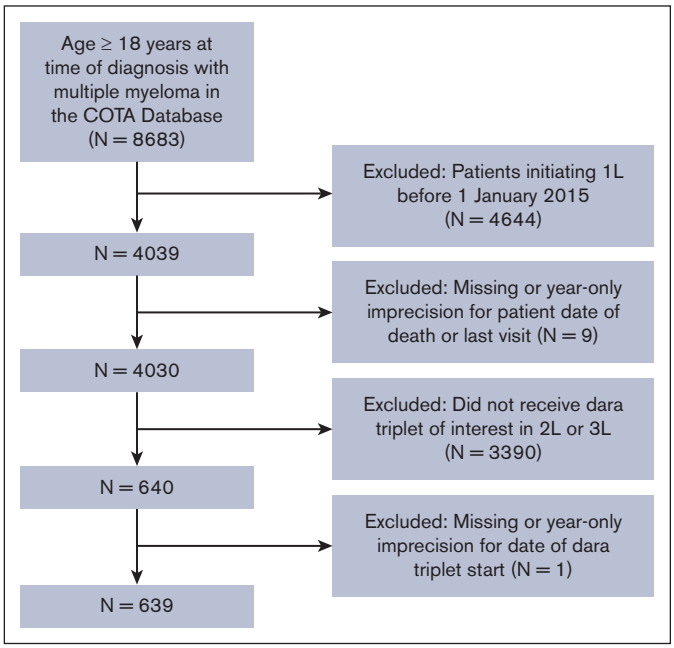

Table 1. Patient and clinical characteristics overall and by treatment group

		Triplet of interest in 2L or 3L therapy		
	Overall (N = 639)	dara-Pd (n = 316)	dara-Kd (n = 122)	dara-Vd (n = 201)
Age at initial Dx, median [IQR], y	66.0 [59.0-73.0]	65.0 [58.0-73.0]	63.0 [56.0-70.0]	68.0 [61.0-75.0]
Sex, n (%)				
Female	271 (42.4)	133 (42.1)	53 (43.4)	85 (42.3)
Male	367 (57.4)	183 (57.9)	69 (56.6)	115 (57.2)
Unknown	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)
Race, n (%)				
Asian	10 (1.6)	5 (1.6)	1 (0.8)	4 (2.0)
Black or African American	91 (14.2)	39 (12.3)	31 (25.4)	21 (10.4)
Other race	84 (13.1)	34 (10.8)	19 (15.6)	31 (15.4)
White	442 (69.2)	230 (72.8)	69 (56.6)	143 (71.1)
Unknown	12 (1.9)	8 (2.5)	2 (1.6)	2 (1.0)
Ethnicity, n (%)				
Hispanic or Latino	98 (15.3)	45 (14.2)	13 (10.7)	40 (19.9)
Not Hispanic or Latino	505 (79.0)	259 (82.0)	102 (83.6)	144 (71.6)
Unknown	36 (5.6)	12 (3.8)	7 (5.7)	17 (8.5)
Practice type, n (%)				
Academic	225 (35.2)	171 (54.1)	32 (26.2)	22 (10.9)
Community	414 (64.8)	145 (45.9)	90 (73.8)	179 (89.1)
LOT of dara triplet, n (%)				
Second	331 (51.8)	127 (63.2)	60 (49.2)	144 (45.6)
Third	308 (48.2)	74 (36.8)	62 (50.8)	172 (54.4)
Time from diagnosis to 2L therapy initiation, median [IQR], mo	16.3 [5.9-31.3]	21.1 [6.3-34.0]	16.4 [6.0-35.9]	12.8 [5.2-24.2]
Follow-up time from 2L therapy initiation, median [IQR], mo	23.9 [11.1-40.3]	26.2 [11.0-41.9]	20.0 [10.7-32.7]	23.3 [11.6-40.3]
Time from end of prior LOT to start of dara triplet LOT, median [IQR], mo	31.0 [14.0-251.5]	38.5 [14.0-425.5]	35.0 [19.0-156.8]	24.0 [13.0-60.0]
Functional risk status, n (%)				
High risk	334 (52.3)	147 (46.5)	64 (52.5)	123 (61.2)
Low risk	305 (47.7)	169 (53.5)	58 (47.5)	78 (38.8)
Cytogenetic risk status, n (%)				
High risk	167 (26.1)	87 (27.5)	42 (34.4)	38 (18.9)
Standard risk	71 (11.1)	45 (14.2)	16 (13.1)	10 (5.0)
Unknown	401 (62.8)	184 (58.2)	64 (52.5)	153 (76.1)
ECOG status, n (%)				
0-1	536 (83.9)	265 (83.9)	104 (85.2)	167 (83.1)
≥2	45 (7.0)	25 (7.9)	5 (4.1)	15 (7.5)
Unknown	58 (9.1)	26 (8.2)	13 (10.7)	19 (9.5)
CCI score, median [IQR]	1.0 [0.0-2.0]	0.0 [0.0-2.0]	0.0 [0.0-2.0]	1.0 [0.0-2.0]

CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group.

Patients in the dara-Vd group had a higher median Charlson Comorbidity Index score (1; IQR, 0-2) than those in the dara-Pd (0; IQR, 0-2) and dara-Kd (0; IQR, 0-2) groups.

Time to next treatment

In the unadjusted analysis, median rwTTNT for dara-Pd was 16.2 months (95% CI, 13.9-19.2). Median rwTTNT for dara-Pd as a 2L therapy was 16.9 months (95% CI, 13.4-25.0) and as 3L therapy was 14.7 months (95% CI, 11.4-20.2). Median unadjusted rwTTNT for dara-Kd was 11.8 months (95% CI, 9.2-17.3), with median rwTTNT of 13.2 months (95% CI, 10.1-21.4) for patients receiving dara-Kd as 2L therapy, and 9.6 months (95% CI, 7.9-18.0) for patients receiving dara-Kd as 3L therapy. Median unadjusted rwTTNT for dara-Vd was 7.8 months (95% CI, 6.3-9.0), with

Table 2. **Prior treatment exposures and refractoriness, overall and by treatment group**

		Triplet of interest in 2L or 3L therapy		
	Overall (N = 639)	dara-Pd (n = 316)	dara-Kd (n = 122)	dara-Vd (n = 201)
Prior lenalidomide treatment, n (%)				
Exposed, not refractory	250 (39.1)	135 (42.7)	58 (47.5)	57 (28.4)
Not exposed	77 (12.1)	18 (5.7)	7 (5.7)	52 (25.9)
Refractory	312 (48.8)	163 (51.6)	57 (46.7)	92 (45.8)
Prior pomalidomide treatment, n (%)				
Exposed, not refractory	10 (1.6)	8 (2.5)	2 (1.6)	0 (0.0)
Not exposed	601 (94.1)	293 (92.7)	112 (91.8)	196 (97.5)
Refractory	28 (4.4)	15 (4.7)	8 (6.6)	5 (2.5)
Prior bortezomib treatment, n (%)				
Exposed, not refractory	262 (41.0)	149 (47.2)	49 (40.2)	64 (31.8)
Not exposed	130 (20.3)	80 (25.3)	20 (16.4)	30 (14.9)
Refractory	247 (38.7)	87 (27.5)	53 (43.4)	107 (53.2)
Prior carfilzomib treatment, n (%)				
Exposed, not refractory	117 (18.3)	85 (26.9)	22 (18.0)	10 (5.0)
Not exposed	461 (72.1)	192 (60.8)	95 (77.9)	174 (86.6)
Refractory	61 (9.5)	39 (12.3)	5 (4.1)	17 (8.5)
Prior daratumumab treatment, n (%)				
Exposed, not refractory	16 (2.5)	4 (1.3)	6 (4.9)	6 (3.0)
Not exposed	583 (91.2)	291 (92.1)	107 (87.7)	185 (92.0)
Refractory	40 (6.3)	21 (6.6)	9 (7.4)	10 (5.0)
SCT exposure before dara triplet, n (%)				
Yes	317 (49.6)	195 (61.7)	69 (56.6)	53 (26.4)
No	322 (50.4)	121 (38.3)	53 (43.4)	148 (73.6)

a median rwTTNT of 8.8 months (95% CI, 6.9-13.8) as 2L therapy and 5.5 months (95% CI, 4.0-8.0) as 3L therapy.

Preplanned unadjusted subgroup analyses of rwTTNT by lenalidomide exposure and refractoriness were also performed. There was no statistically significant difference in rwTTNT by lenalidomide exposure or by lenalidomide refractoriness or relapsed disease. When stratifying by functional risk (standard risk vs high risk), rwTTNT and rwOS were generally similar across all 3 regimens. For dara-Pd administered as 2L therapy, there was a statistically longer unadjusted rwTTNT (median, 9.7 vs 18.9 months; HR, 0.52; 95% CI, 0.32-0.83) and rwOS (median, 27.9 vs not reached; HR, 0.34; 95% CI, 0.17-0.67) for functional standard risk vs high risk disease.

Comparisons between the different regimens of interest were performed using a tIPTW analysis, as described in "Methods" (Fig. 2). dara-Vd was associated with inferior rwTTNT compared with both dara-Kd and dara-Pd. In comparing dara-Vd with dara-Kd, median rwTTNT for dara-Vd was 7.6 months (95% CI, 6.2-8.6) and was 12.9 months (95% CI, 10.7-16.4) for dara-Kd (HR, 0.70; 95% CI, 0.49-0.99; Table 3). In comparing dara-Vd with dara-Pd, median rwTTNT for dara-Vd was 6.9 months (95% CI, 6.0-8.0) and 15.3 months (95% CI, 13.6-17.2) for dara-Pd (HR, 0.57; 95% CI, 0.43-0.77). Median rwTTNT were similar for dara-Pd (15.7 months; 95% CI, 13.9-18.5) and dara-Kd (13.2 months; 95% CI, 10.7-16.4) after tIPTW adjustment (HR, 1.1; 95% CI, 0.8-1.6).

OS

Median rwOS for the entire cohort was 37.9 months (95% CI, 32.9-43.9) over a median follow-up time from initiation of dara triplet LOT of 25.5 months (95% CI, 24.1-27.5). Median unadjusted rwOS for dara-Pd was 43.5 months (95% CI, 39.8-49.7) with a median follow-up time from the initiation of the dara triplet LOT of 24.4 months (95% CI, 21.6-27.7), and median rwOS for dara-Kd was not reached (95% CI, 22.6 to not reached) over a median follow-up of 19.2 months (95% CI, 16.1-22.0) from the initiation of the dara triplet LOT. Over a 38.1-month follow-up time from dara triplet LOT initiation, median unadjusted rwOS for dara-Vd was 32.0 months (95% CI, 23.3-37.7).

In the tIPTW adjusted analysis comparing regimens head-to-head (Fig. 3), no regimen was found to be significantly associated with superior rwOS. Notably, the dara-Pd group had a numerically higher rwOS compared with dara-Vd (median, 43.0 vs 32.0 months; Table 3).

Discussion

This is the first study, to our knowledge, to directly compare the effectiveness of 3 commonly used dara-based triplets in the rw treatment of RRMM. In this tIPTW adjusted rw analysis that accounts for imbalances in key patient and disease characteristics

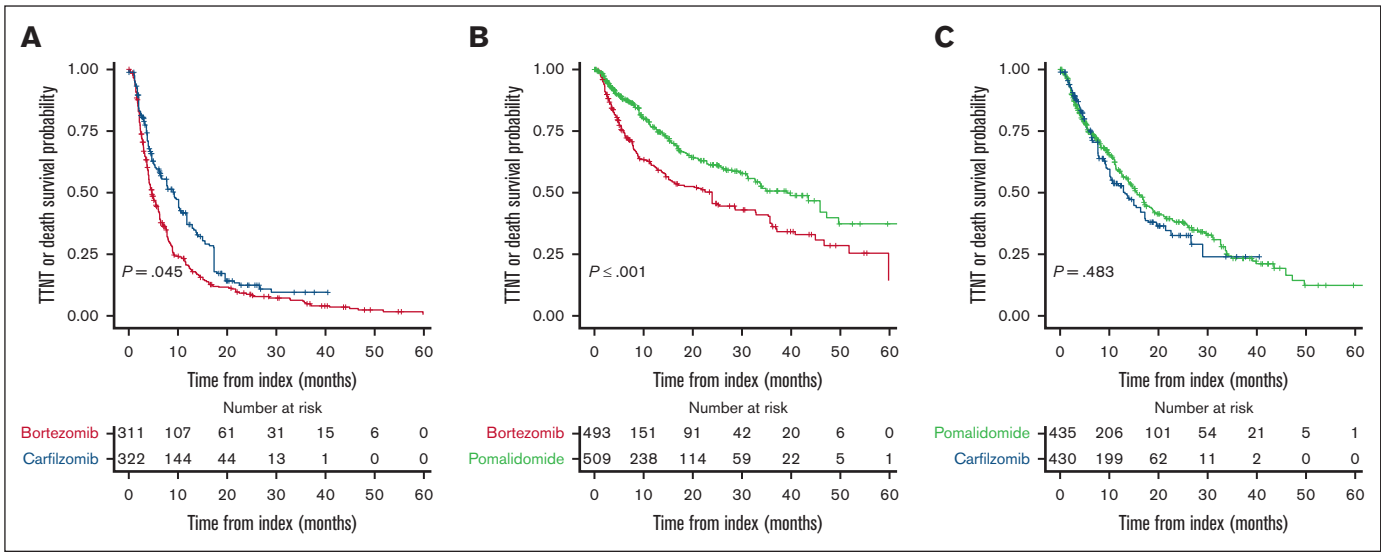

Figure 2. Adjusted rwTTNT. Adjusted rwTTNT for (A) dara-Kd (blue) vs dara-Vd (red), (B) dara-Pd (green) vs dara-Vd (red), and (C) dara-Kd (blue) vs dara-Pd (green). The number at risk, using IPTW methodology, calculates the probability of exposure to a given treatment group based on a patient's characteristics. The calculated weights (the inverse of the propensity score) are applied to the study population, thereby creating a pseudopopulation with equally distributed confounders across both groups. Therefore, the "n" of the pseudopopulation is greater than that of the original population.

among treatment groups, we showed that dara-Vd was associated with inferior rwTTNT compared with both dara-Kd and dara-Pd when used as 2L or 3L therapy. We also did not find significant rwTTNT differences between dara-Kd and dara-Pd; based on initial power calculations, the study likely did not have sufficient sample size to detect differences between these 2 treatment groups.

It is important to put these data into context with previously published studies. Importantly, clinical trials typically use PFS as an end point of interest. In rw studies, rwTTNT is often used as a surrogate, because it is assumed that a patient would not initiate new therapy unless progressive disease was present.[13] As such, we compare median rwTTNT from our study with PFS in the pivotal trials mentioned hereafter. The phase 3 CASTOR trial compared dara-Vd with Vd, wherein treatment with dara-Vd resulted in a median PFS of 16.7 months.[2,14,15] Notably, only 24% of the patients receiving dara-Vd had lenalidomide-refractory disease, with nearly all (90%) having received ≥2 prior lines of therapy; median PFS for this subgroup was 7.8 months.[2,14] Median rwTTNT for all patients receiving dara-Vd in our analysis was 7.8 months, with 46% of patients being classified as being lenalidomide refractory; however, 61% of patients in this treatment group had functional high-risk disease, and 18.9% had cytogenetic high-risk disease (76.1% unknown). The risk profile of this treatment group may have contributed to the difference between the CASTOR trial PFS and rwTTNT in this study; although importantly, there were no significant differences in rwTTNT based on functional risk in our dara-Vd group. Additionally, dosing information was not analyzed in this rw study. Bortezomib was studied in the CASTOR trial as a twice weekly regimen[14]; once weekly regimens are more common in the real world, although there does not appear to be a difference in outcomes between these strategies in the frontline setting.[16]

Table 3. Prior treatment exposures and refractoriness, overall and by treatment group

		TTNT			OS		
Adjusted TTNT and OS	**N**	**TTNT events**	**Median (95% CI)**	**HR (95% CI)**	**OS events**	**Median (95% CI)**	**HR (95% CI)**
Bortezomib vs carfilzomib							
dara-Vd	311.49	244.08	7.59 (6.21-8.55)	ref	153.99	32.65 (27.16-37.71)	ref
dara-Kd	321.82	189.60	12.89 (10.65-16.37)	0.70 (0.49-0.99)	111.08	26.14 (22.22-NR)	0.94 (0.59-1.5)
Bortezomib vs pomalidomide							
dara-Vd	492.61	365.60	6.94 (5.98-7.96)	ref	234.31	32.02 (25.12-36.1)	ref
dara-Pd	509.25	281.77	15.25 (13.61-17.16)	0.57 (0.43-0.77)	162.88	42.97 (37.94-47.21)	0.75 (0.51-1.1)
Pomalidomide vs Carfilzomib							
dara-Pd	434.64	237.78	15.68 (13.91-18.54)	ref	138.27	42.97 (37.94-47.24)	ref
dara-Kd	429.87	228.32	13.18 (10.65-16.37)	1.13 (0.8-1.6)	97.38	NR (28.14-NR)	0.96 (0.60-1.53)

NR, not reached; ref, reference.

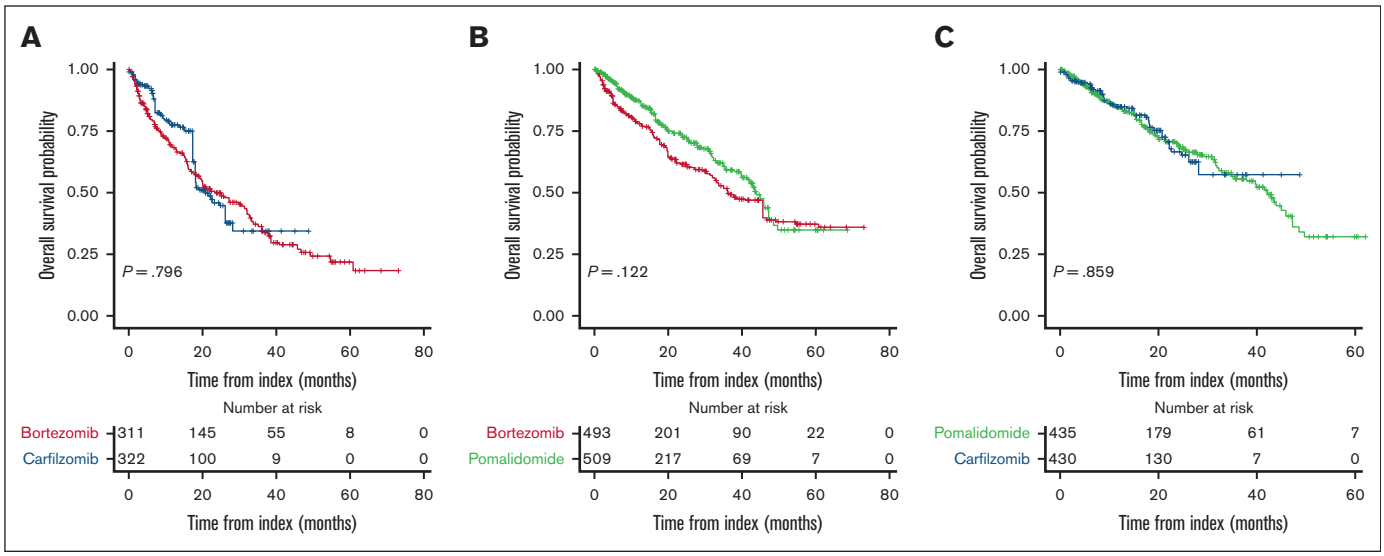

Figure 3. Adjusted rwOS. Adjusted rwOS for (A) dara-Kd (blue) vs dara-Vd (red), (B) dara-Pd (green) vs dara-Vd (red), and (C) dara-Kd (blue) vs dara-Pd (green). The number at risk is calculated using the same methodology as for rwTTNT.

The phase 3 APOLLO study compared dara-Pd with Pd, and found median PFS with dara-Pd to be 12.4 months, including 79% of patients who were lenalidomide refractory and with a median of 2 prior lines of therapy.[6,7] This is in stark contrast to a nonrandomized phase 2 study of dara-Pd (75% of patients were lenalidomide refractory; 63% had 1 prior LOT) that reported a median PFS of 30.8 months.[17] Median rwTTNT for dara-Pd in our study was 16.2 months, although only 52% of patients had documented lenalidomide refractoriness. Pomalidomide dosing in the real world is also typically lower than phase-3 dosing, the effect of which is unknown.[18]

The phase 3 CANDOR trial evaluated twice-weekly dara-Kd vs Kd in patients with 1 to 3 prior lines of therapy; 39% of patients in this study were lenalidomide exposed and 32% were lenalidomide refractory.[4] Median PFS was 28.6 months for dara-Kd overall and 28.1 months in lenalidomide-refractory disease, with similar effect sizes.[4] This is where our results differed the most from historical data; median rwTTNT for dara-Kd was 11.8 months. Notably, the dara-Kd group in our data set comprised patients with higher-risk features than patients in the CANDOR study. Despite a high degree of missingness for cytogenetic data in our data set, there were more patients with high-risk cytogenetics (34%) than in the CANDOR study (15%)[4]; notably, there were no significant differences in rwTTNT when stratified by functional risk in our analysis. Although CANDOR used twice weekly carfilzomib at 56 mg/m^2, dosing of carfilzomib may have also been different in the rw setting. Some clinicians may have assigned carfilzomib 27 mg/m^2 twice weekly to patients; a randomized phase 2 study comparing 27 and 56 mg/m^2 twice weekly found no statistical differences in response rate or PFS.[19] Others may have assigned once weekly carfilzomib 56 to 70 mg/m^2; a post hoc analysis found that once weekly carfilzomib 70 mg/m^2 led to similar overall response rates and PFS as twice weekly carfilzomib 56 mg/m^2.[20] Recent evidence in the newly diagnosed setting have found excellent results with the use of carfilzomib 56 mg/m^2 weekly as part of a "quadruplet" induction regimen.[21,22]

This study population appears to have been enriched for patients with high-risk disease features. Compared with the aforementioned trials involving dara-based triplets, this analysis included a greater proportion of patients with functional high-risk disease (52%) and cytogenetic high-risk disease (26%, which is likely an underestimate, considering that 63% had unknown cytogenetic risk status). This could be because of the requirement for patients to have initiated 2L and/or 3L therapy to qualify for this study population. By nature of requiring later lines of therapy within a specified amount of time, we may have selected for a particularly high-risk rw population, compared with the general MM population in the United States; this may have negatively affected the rw outcomes but there were no significant differences in outcomes between patients with functional high risk and standard risk for any of the assessed regimens.

Limitations of this study are primarily related to nuances in rw patient care. Specifically, diagnostic testing and clinical care may not be uniform in the rw setting. Unlike clinical trials with predefined study outcomes and assessment schedules, rw clinical practices may not be consistent across patients or physicians. Although chemotherapies assigned to patients were captured in the COTA database, doses and dose schedules of therapies were not available. Refractoriness to therapies may have been underestimated because of unclear or missing documentation for reasons of discontinuation in EHRs. Additionally, although the COTA database contains detailed information about a patient's treatment journey, and most patients with cancer receive most of their care within a network, care delivered by facilities outside the COTA network may not be captured. In the rw practice setting, mortality data are not typically reported according to the same requirements as in clinical trials. As such, COTA addresses potential gaps in mortality reporting using a composite mortality variable. Because of potential variability in the documentation of response and progression events for patients with MM in RWD sources as compared with the strict assessment schedules and application of International Myeloma Working Group criteria in

randomized controlled trials, rwTTNT and rwOS were chosen as end points rather than depth of response, duration of response, or PFS. Although this, to our knowledge, is the largest rw analysis of dara-based triplets reported, our study may have been underpowered to detect rwTTNT and rwOS differences because of small sample sizes. Lastly, because the MM treatment paradigm is rapidly evolving, all potential anti-CD38 monoclonal antibody–based therapies of interest were not analyzed in this study (ie, isatuximab-based triplets). Furthermore, the incorporation of dara into frontline induction therapy and variable use in maintenance may result in uncertain use and efficacy of dara in later lines.

The strengths of this study relate to the comprehensiveness and longitudinal nature of the COTA rw database. The COTA database contains relevant diagnostic, clinical, and outcome data associated with a patient's MM treatment journey. RWD sources enhance understanding of the patient population and inform on the generalizability of the results observed in the clinical trial setting. Additionally, our analysis is the first, to our knowledge, to compare these dara-based combinations directly and with robust sample size. Although McMillan et al published a larger study of rw use of dara-Vd with 296 patients (compared with 201 in this analysis), our study also provides data on other regimens and is a more representative population with respect to prior lenalidomide exposure (15% in McMillan et al vs 87.9% in our analysis).

In this representative US population of patients with RRMM receiving 2L or 3L therapy with a dara-based triplet, dara-Vd was associated with inferior rwTTNT and, possibly, rwOS. Despite differences in the timing of approvals of these dara-based triplets, our analysis shows a clear clinician and/or patient preference for dara-Pd, likely owing to the convenience and expected favorable toxicity profile of the regimen. Phase 3 data with dara-Kd have shown 1 of the longest durations of PFS in RRMM, although this finding is not confirmed by our analysis.

Our study provides valuable head-to-head comparisons of 3 potential regimens to be used in the 2L or 3L setting and suggests that future randomized phase 3 trials, with the exception of those meant to isolate the potential efficacy of an agent added to Vd or dara-Vd, should not use dara-Vd as a comparator arm to reflect the best possible standard of care. The KarMMA-3 study comparing idecabtagene vicleucel with standard of care in the RRMM setting allowed for dara-Vd or dara-Pd to be used in the standard of care arm among other options; only 5% of patients received dara-Vd whereas 33% received dara-Pd, suggesting a preference for the latter regimen.[23] There are still 2 other phase 3 studies that assign some, or all, patients in the control arm to dara-Vd (ClinicalTrials.gov identifier: NCT05083169 and NCT04975997, respectively); consideration should be given to amend these trials to allow access to a better standard of care. Although further exploration of the effect of weekly dosing strategies of carfilzomib in the real world is needed, the results of our rw analysis suggest that both dara-Pd and dara-Kd represent appropriate and reasonable comparators in current and future trials.

Authorship

Contribution: B.A.D. was responsible for the study concept; all authors were responsible for statistical design and analysis; and all authors were responsible for manuscript drafting and revisions.

Conflict-of-interest disclosure: B.A.D. declares advisory board fees from Janssen and COTA, Inc; and serves as an independent trial reviewer for Bristol Myers Squibb. J.A., L.L.F., C.M.Z., E.H., A.J.B., and C.-K.W. are employees of, and own stock in, COTA, Inc.

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