Title

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Journal

Journal of managed care & specialty pharmacy, 29(11)

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Publication Date

2023-11-01

DOI

10.18553/jmcp.2023.23031

Peer reviewed

Comparison of health care costs and resource utilization for commonly used proteasome inhibitor–immunomodulatory drug-based triplet regimens for the management of patients with relapsed/refractory multiple myeloma in the United States

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Plain language summary

Relapsed/refractory myeloma (RRMM) is an incurable cancer of the plasma cells with significant financial impact. This study compared health care costs and resource use among patients with RRMM treated with standard-of-care regimens of proteasome inhibitors (bortezomib [V], ixazomib [I], carfilzomib [K]), plus lenalidomide-dexamethasone (Rd). Non–drug-related costs were an important driver of total health care costs. Even after excluding treatment administration costs, patients treated with IRd and VRd had significant medical cost savings compared with those treated with KRd.

Implications for managed care pharmacy

Although novel therapies have improved survival in RRMM, there is a need to manage rising costs of care. In this real-world study, medical expenses were a key driver of the health care costs associated with proteasome inhibitor–based RRMM therapies. Furthermore, specific regimens were associated with medical cost savings even after excluding treatment administration costs. These findings may help to inform MM treatment strategies while reducing non–drug-related costs.

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J Manag Care Spec Pharm.
2023;29(11):1205-218

ABSTRACT

BACKGROUND: Economic differences among currently available proteasome inhibitors (PI)-based lenalidomide-dexamethasone (Rd)-backbone triplet regimens—ixazomib (I), bortezomib (V), and carfilzomib (K) plus Rd—remain poorly understood.

OBJECTIVE: To assess health care resource utilization (HCRU) and health care costs of patients with relapsed/refractory multiple myeloma (RRMM) in the United States treated with IRd, VRd, and KRd.

METHODS: This retrospective longitudinal cohort study using IQVIA PharMetrics Plus adjudicated claims US data (January 1, 2015, to September 30, 2020) included adult patients with all available data who initiated IRd, VRd, or KRd in second line of therapy or later (LOT2+) on or after September 1, 2015. The index date was the treatment initiation date for each LOT (multiple LOTs per patient were included) and the baseline was 6 months pre-index. MM-related and all-cause HCRU/costs were assessed during follow-up and reported per patient per month (PPPM; 2020 US Dollars). For MM-related costs only, treatment administration costs were excluded from outpatient (OP) costs and instead summed with pharmacy costs. HCRU/costs were compared between treatment groups using generalized linear models (GLMs). Cost variables were compared using 2-part

models and GLM with log transformation and γ distribution. Inverse probability of treatment weighting (IPTW) adjusted for imbalance of baseline confounders across treatment groups.

RESULTS: The study included 511 patients contributing 542 LOTs (IRd: n = 153; VRd: n = 262; KRd: n = 127). Before IPTW, mean observed time spent on therapy was 8.5, 9.3, and 7.3 months for the IRd, VRd, and KRd cohorts, respectively. During follow-up and after IPTW, IRd and VRd were associated with significantly fewer OP visits vs KRd. Post-IPTW comparisons of MM-related costs for IRd vs KRd yielded lower OP costs for IRd (mean diff. PPPM: –$3,428; $P < 0.001$), contributing to lower total medical costs (–$3,813; $P < 0.001$) and total health care cost savings with IRd vs KRd (–$5,813; $P = 0.001$). MM-related OP costs were lower for VRd (mean diff. PPPM: –$3,543; $P < 0.001$) than KRd, reducing its total MM-related medical costs (–$3,997; $P = 0.002$), leading to total MM-related health care cost savings with VRd vs KRd (–$12,357; $P < 0.001$). All-cause cost comparisons yielded similar results (total health care cost savings for IRd and VRd vs KRd: –$6,371 and –$13,629, respectively; all $P < 0.001$).

CONCLUSIONS: From the US insurance-payer perspective, patients treated with IRd and VRd had significant medical cost savings vs KRd due to lower OP costs when excluding treatment administration costs. The differential economic impacts of PI-Rd regimens in this study may help to inform treatment decisions for patients with MM.

Multiple myeloma (MM) is a blood cancer that impairs plasma cell multiplication and accumulation in bone marrow, leading to bone destruction and marrow failure.[1] In the United States, MM accounted for 1.8% of all new cancer cases in 2021, with an annual incidence rate of 7.1 per 100 000.[2] The median age of patients at diagnosis is approximately 70 years, with 37% of patients aged younger than 65 years.[3] Over the past decade, the introduction of new MM therapies has prolonged survival among patients.[4] However, the cost of care has also increased over time,[4,5] and may be especially pronounced among patients with relapsed/refractory MM (RRMM).[6]

Among the newer therapies for MM, proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) such as lenalidomide have significantly improved prognosis.[7,8] Currently, 3 PIs have been approved for the treatment of MM, including ixazomib (I; oral), bortezomib (V; intravenous or subcutaneous), and carfilzomib (K; intravenous).[9-13] These PIs are commonly combined with lenalidomide-dexamethasone (Rd) to form triplet regimens, which are associated with superior clinical outcomes when compared with doublet regimens.[14-17] Accordingly, current clinical practice guidelines recommend some PI-containing Rd-backbone triplet regimens for the treatment of patients with RRMM in certain instances.[18,19] In particular, IRd and KRd are considered an effective intervention for this patient population[18,19] based on phase 3 clinical trials.[14,15,19]

Despite the efficacy of PI-containing Rd-backbone triplet regimens for MM, large-scale clinical trials comparing these regimens head to head in the RRMM setting are lacking, and heterogeneity in study populations across trials could make the comparisons unreliable. Furthermore, there are limited real-world data on the comparative effectiveness and costs associated with PI-containing RRMM treatments and, in turn, the value of these therapies to payers. To supplement the findings from studies evaluating the clinical impact of PI-containing RRMM regimens, we conducted a retrospective longitudinal study evaluating health care resource utilization (HCRU) and health care costs from a payer perspective among patients with RRMM in the United States treated with IRd, VRd, and KRd.

Methods

DATA SOURCE

The present study used data spanning from January 1, 2015, to September 30, 2020, from IQVIA PharMetrics Plus adjudicated claims US data, which holds fully adjudicated claims data on approximately 40 million patients covering a diverse representation of employers, payers, and providers across all 50 states. The enrollee population in the IQVIA PharMetrics Plus adjudicated claims US data are generally representative of the commercially insured population in the United States with respect to both age and sex, although approximately 1% of the enrollees are covered by Medicare Advantage plans. IQVIA PharMetrics Plus adjudicated claims US data includes demographic measures such as age, sex and plan type, inpatient and outpatient claims, and diagnoses and procedures based on *International Classification of Diseases, Ninth Revision* (ICD-9), *Tenth Revision* (ICD-10), and Current Procedural Terminology (CPT) codes, as well as their associated costs, including the paid amount (ie, the funds paid to the provider by the plan), which was used in the present analysis. Date of death and actual start and end dates of treatment were not available. Treatment dates were approximated by date of claims and days of supply. Data used in this study were de-identified and compliant with the Health Insurance Portability and Accountability Act of 1996; therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4).

STUDY DESIGN AND POPULATION

A retrospective longitudinal observational cohort study was conducted to address the study objectives. The study design scheme is depicted in Supplementary Figure 1 (available in online article).

The index date was defined as the date of initiation of PI-based Rd-backbone triplet therapies of interest (ie, first

claim for the therapy) in second line of therapy (LOT2) or later. The *baseline period* was defined as the 6-month period of continuous health plan enrollment prior to the index date. The *observation period* spanned from the index date to end of observation, defined as the earliest of end of continuous health plan enrollment or data availability (ie, September 30, 2020). A *washout period*, defined as the 3-month period prior to the date of first observed MM diagnosis from the start of available data, was used to identify patients with newly diagnosed MM. KRd was the reference group with which IRd and VRd were compared, and in addition IRd was compared with VRd.

The study included patients who had at least 1 medical claim with a primary or secondary diagnosis of MM (ICD-9-CM: 203.0x; ICD-10-CM: C90.0x) during the study period and who were aged 18 years or older at first observed MM diagnosis. Eligible patients had initiated IRd, VRd, or KRd in LOT2 or later on or after September 1, 2015 (defined as the index LOT), and were further required to have 2 or more medical or pharmacy claims on different days. Because of the potential harm of long-term steroid use,[20] some patients may have received steroid-sparing regimens; therefore, patients on either triplet or doublet therapy were included. Additionally, eligible patients were required to have continuous health plan enrollment for at least 3 months preceding the first observed diagnosis of MM (ie, washout period). Patients with evidence of anticancer MM treatment or stem cell transplant (Supplementary Table 1) during the washout period were excluded to ensure that the study population consisted of patients with newly diagnosed MM to reliably determine RRMM status and LOT. The unit of analysis was patient LOT and multiple LOTs per patient, including retreatment of the same regimen, were included in the analysis to accurately reflect patients' treatment journeys and outcomes. Treatment cohorts were defined by type of regimens received in each LOT.

Due to the lack of progression information in claims data, a patient was deemed to have RRMM if they had received at least 2 LOTs for MM. These LOTs were identified using an established MM LOT algorithm developed in previous electronic health records (EHR) database studies[21–23] and were adapted for the current claims database analysis to account for differences in data structure and availability.

STUDY MEASURES AND OUTCOMES

Patients' demographic and clinical characteristics were assessed during the baseline period. Clinical characteristics included CRAB (calcium [elevated] or hypercalcemia, renal insufficiency/impairment, anemia, bone lesions/bone disease/skeletal related events) symptoms (Supplementary Table 2 for diagnosis and procedure codes),[21,24] Charlson comorbidity index (CCI) excluding MM diagnosis (Supplementary Table 3 for diagnosis and procedure codes),[25] additional MM-related comorbidities (Supplementary Table 4 for diagnosis codes), derived frailty status (frail, intermediate, fit; determined by age and CCI),[21,26] LOT number, prior stem cell transplant, prior exposure and refractory status to treatments (eg, PIs, IMIDs, and lenalidomide), time from first observed MM diagnosis to index date, and baseline total MM-related and all-cause health care costs. Observed time spent on therapy was reported among our original sample based on the date of claims and pharmacy dispensing.

MM-related and all-cause HCRU and health care costs incurred during each LOT were evaluated post-index by treatment cohort. MM-related HCRU was defined as health care encounters on days with at least 1 medical claim with a primary or secondary diagnosis for MM, and comprised hospitalizations and hospitalization days, outpatient (OP) visits, emergency department (ED) visits, and other visits (eg, nursing facility and long-term care). MM-related OP visits included visits for MM-treatment administration, defined as MM-related OP encounters with a procedure code for MM-treatment administrations, and visits not related to MM-treatment administration. All-cause HCRU was defined as health care encounters due to any cause and included similar components to those mentioned above.

MM-related total health care costs were composed of total medical costs from claims with at least 1 diagnosis of MM, including hospitalization costs, OP costs, ED costs, and other costs, as well as costs related to pharmacy and OP treatment administration. Regarding the latter costs, fully oral MM treatments such as IRd may be billed exclusively to a pharmacy benefit, whereas costs for VRd and KRd may be partly billed to a medical benefit owing to the need for OP intravenous or subcutaneous administration of V and K. Thus, expenses associated with MM-treatment administration were excluded from MM-related OP costs and instead summed with MM-related pharmacy costs. This was done to reflect the costs associated with MM treatment while accounting for the different billing practices across PIs due to varied routes of administration (with respect to MM-related HCRU, OP visits for MM-treatment administration were not summed with pharmacy-related visits, as the latter outcome was not assessed in this study). Total all-cause health care costs included the same cost components as mentioned above, except that OP costs included expenses related to OP visits for MM-treatment administration, and pharmacy costs included costs for MM medications.

STATISTICAL ANALYSIS

To adjust for potential confounding due to differences in baseline characteristics between cohorts, inverse

probability of treatment weighting (IPTW) was conducted separately for each comparison of HCRU and costs between PI-based Rd triplet regimens.[27] Weights were calculated for each pairwise comparison based on a propensity score (PS), defined as the probability of receiving the index regimen (vs reference regimen) given a set of baseline covariates that were imbalanced at baseline. IPTW weights were calculated separately for each comparison as 1/PS for the index regimen and 1/(1-PS) for the reference regimen. To enhance precision in the effect estimates of the outcomes, IPTW was stabilized by the marginal probability of receiving the index regimen. The distribution of the weights was examined and truncated at the first and 99th percentile to reduce the impact of extreme weights.[27]

Baseline characteristics were described for each treatment cohort using frequencies and proportions for categorical variables and means, SDs, medians, and interquartile ranges for continuous variables. For each comparison, the distribution of baseline characteristics was compared in the weighted and unweighted cohorts using standardized differences, with greater than or equal to 10% difference indicating imbalance.[28] Characteristics that remained imbalanced after weighting were included in the IPTW-weighted multivariable regression models for a doubly robust approach.[29]

MM-related and all-cause HCRU were described for each treatment cohort as incidence rates per patient-month (PPM), which were calculated as the total number of encounters during the LOT divided by the observed length of follow-up in that LOT (ie, total patient-months of observation while on the treatment with a given PI-Rd triplet). To compare HCRU between the treatment cohorts of interest, incidence rate ratios (IRRs) were estimated using IPTW-weighted multivariable generalized linear models (GLM) with a Poisson distribution. Robust sandwich estimators were used to account for within-subjects correlation and to derive the 95% CIs and *P* values ($P < 0.05$ was statistically significant) because a patient could contribute multiple LOTs.

MM-related and all-cause health care costs were described during the LOT for each treatment cohort using means and 95% CI on a per-patient-per-month (PPPM) basis, which were calculated as the monthly costs per patient and then aggregated across all patients. All costs were inflation-adjusted to 2020 US dollars based on the medical care component of the Consumer Price Index. Mean cost differences between cohorts were estimated using IPTW-weighted multivariable GLM with a □ distribution and log link. Robust sandwich estimators were used to account for within-subjects correlation and to derive the 95% CIs and *P* values. For health care cost variables with a substantial proportion of patients that had costs equal to zero (ie, MM-related and all-cause hospitalization costs, ED costs, other costs, and MM-related OP costs), two-part models with a logistic regression model (for estimating the probability of observing a nonzero cost outcome) and a GLM with a □ distribution and a log-link function, weighted by stabilized IPTW and adjusted for key confounders were used. Nonparametric bootstrap procedures were used to estimate 95% CIs and *P* values.

All statistical analyses were conducted using SAS Enterprise Guide 7.1 software (SAS Institute).

Results

A total of 511 patients initiated on IRd, VRd, and KRd were included in the study and contributed to 542 distinct LOTs (IRd: n = 153; VRd: n = 262; KRd: n = 127) (Supplementary Figure 2).

BASELINE CHARACTERISTICS

Demographic and clinical characteristics for the original sample of patients with RRMM before IPTW are shown in Table 1. In the original sample, the median observed time spent on therapy was 5.2 months, 5.9 months, and 4.8 months for the IRd, VRd, and KRd cohorts, respectively. The median age in years of the KRd cohort (59.0 years) was lower than that of the IRd and VRd cohorts (61.0 and 62.0 years; std. diff. 50.6% and 50.6%). The KRd cohort also had a lower proportion of female patients (39.4%) relative to the IRd cohort (47.1%; std. diff. = 15.6%) and VRd cohorts (50.4%; std. diff. = 22.3%). The majority of patients in the unweighted IRd, VRd, and KRd cohorts were commercially insured, and resided in the South of the United States.

The proportion of patients with CRAB symptoms was similarly high across the 3 cohorts (IRd: 79.7%, VRd: 85.1%, KRd: 85.8%), with the most commonly reported symptom being anemia (IRd: 64.1%, VRd: 66.8%, KRd: 74.0%). The median CCI score was comparable across cohorts (all 2.0) and MM-related comorbidities were present in the majority of patients (IRd: 79.9%, VRd: 87.8%, KRd: 81.9%). In terms of frailty status, the majority of the patients were intermediate fit (IRd: 51.0%, VRd: 61.8%, KRd: 59.1%) followed by fit (IRd: 40.5%, VRd: 29.4%, KRd: 38.6%). The proportion of frail patients was lower in the KRd cohort (2.4%) relative to the IRd cohort (8.5%; std. diff.: 27.3%) and VRd cohort (8.8%; std. diff.: 28.3%). The proportion of patients with refractory status to PIs was significantly higher in the IRd cohort (49.0%) and the KRd cohort (53.5%) compared with the VRd cohort (5.0%).

The median total all-cause health care costs during the baseline period were higher for the KRd cohort ($118,485) compared with the IRd cohort ($100,662; std. diff.: 29.7%)

TABLE 1 Baseline Characteristics of Patients With RRMM in the Original Sample: IRd vs KRd and VRd vs KRd

	IRd (N=153)	KRd (N=127)	Std Diff (%)[a]	VRd (N=262)	KRd (N=127)	Std Diff (%)[a]
Age at index date,[b] years						
Mean ± SD	62.4 ± 10.3	57.6 ± 8.5	50.6*	62.2 ± 9.7	57.6 ± 8.5	50.6*
Median (IQR)	61.0 (55.0-69.0)	59.0 (53.0-63.0)	—	62.0 (56.0-68.0)	59.0 (53.0-63.0)	—
Sex, n (%)						
Male	81 (52.9)	77 (60.6)	15.6*	130 (49.6)	77 (60.6)	22.3*
Female	72 (47.1)	50 (39.4)	15.6*	132 (50.4)	50 (39.4)	22.3*
Geographic region, n (%)						
South	65 (42.5)	69 (54.3)	23.9*	114 (43.5)	69 (54.3)	21.8*
Northeast	34 (22.2)	16 (12.6)	25.6*	53 (20.2)	27 (21.3)	2.5
West	29 (19.0)	14 (11.0)	22.4*	52 (19.8)	16 (12.6)	19.8*
Midwest	25 (16.3)	27 (21.3)	12.6*	43 (16.4)	14 (11.0)	15.7*
Other	0 (0.0)	0 (0.0)	0.0	0 (0.0)	0 (0.0)	0.0
Unknown	0 (0.0)	1 (0.8)	12.6*	0 (0.0)	1 (0.8)	12.6*
Insurance payer type, n (%)						
Commercial	78 (51.0)	78 (61.4)	21.2*	133 (50.8)	78 (61.4)	21.6*
Self-insured[c]	43 (28.1)	43 (33.9)	12.5*	90 (34.4)	43 (33.9)	1.0
Medicare Advantage or supplemental	31 (20.3)	5 (3.9)	51.7*	37 (14.1)	5 (3.9)	36.1*
Other[d]	1 (0.7)	0 (0.0)	11.5*	1 (0.4)	0 (0.0)	8.8
Unknown	0 (0.0)	1 (0.8)	12.6*	1 (0.4)	1 (0.8)	5.3
Index year, n (%)						
2015	0 (0.0)	0 (0.0)	0.0	16 (6.1)	0 (0.0)	36.1*
2016	16 (10.5)	22 (17.3)	20.0*	54 (20.6)	22 (17.3)	8.4
2017	38 (24.8)	30 (23.6)	2.8	62 (23.7)	30 (23.6)	0.1
2018	32 (20.9)	32 (25.2)	10.2*	48 (18.3)	32 (25.2)	16.7*
2019	36 (23.5)	24 (18.9)	11.4*	50 (19.1)	24 (18.9)	0.5
2020	31 (20.3)	19 (15.0)	14.0*	32 (12.2)	19 (15.0)	8.0
CRAB symptoms,[e,f] n (%)						
Any	122 (79.7)	109 (85.8)	16.2*	223 (85.1)	109 (85.8)	2.0
Anemia	98 (64.1)	94 (74.0)	21.7*	175 (66.8)	94 (74.0)	15.9*
Renal insufficiency/impairment	52 (34.0)	52 (40.9)	14.4*	118 (45.0)	52 (40.9)	8.3
Bone disease	41 (26.8)	30 (23.6)	7.3	95 (36.3)	30 (23.6)	27.9*
Hypercalcemia	18 (11.8)	11 (8.7)	10.3*	35 (13.4)	11 (8.7)	15.1*
Charlson comorbidity index[f]						
Mean ± SD	2.7 ± 2.9	3.1 ± 2.9	12.8*	3.3 ± 2.8	3.1 ± 2.9	9.3
Median (IQR)	2.0 (0.0-6.0)	2.0 (0.0-6.0)	—	2.0 (1.0-6.0)	2.0 (0.0-6.0)	—
MM-related comorbidities,[e,f] n (%)						
Any	122 (79.7)	104 (81.9)	5.5	230 (87.8)	104 (81.9)	16.5*
Hypertension	73 (47.7)	56 (44.1)	7.3	159 (60.7)	56 (44.1)	33.7*
Chronic pain/fibromyalgia	39 (25.5)	43 (33.9)	18.4*	107 (40.8)	35 (27.6)	28.3*

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TABLE 1 Baseline Characteristics of Patients With RRMM in the Original Sample: IRd vs KRd and VRd vs KRd (*continued*)

	IRd (N = 153)	KRd (N = 127)	Std Diff (%)[a]	VRd (N = 262)	KRd (N = 127)	Std Diff (%)[a]
Neutropenia	38 (24.8)	41 (32.3)	16.5*	69 (26.3)	43 (33.9)	16.5*
Monoclonal gammopathy	36 (23.5)	35 (27.6)	9.3	48 (18.3)	41 (32.3)	32.5*
Thrombocytopenia	31 (20.3)	41 (32.3)	27.6*	47 (17.9)	41 (32.3)	33.5*
Lymphopenia and/or leukopenia	4 (2.6)	7 (5.5)	14.7*	18 (6.9)	7 (5.5)	5.6
Peripheral neuropathy	0 (0.0)	4 (3.1)	25.5*	1 (0.4)	4 (3.1)	21.1*
Frailty status,[g] n (%)						
Fit	62 (40.5)	49 (38.6)	4.0	77 (29.4)	49 (38.6)	19.5*
Intermediate	78 (51.0)	75 (59.1)	16.3*	162 (61.8)	75 (59.1)	5.7
Frail	13 (8.5)	3 (2.4)	27.3*	23 (8.8)	3 (2.4)	28.3*
LOT number, n (%)						
2	109 (71.2)	85 (66.9)	9.3	208 (79.4)	85 (66.9)	28.4*
3	34 (22.2)	30 (23.6)	3.3	39 (14.9)	30 (23.6)	22.3*
≥4	10 (6.5)	12 (9.4)	10.8*	15 (5.7)	12 (9.4)	14.1*
Prior exposure to a PI, n (%)	124 (81.0)	106 (83.5)	6.3	185 (70.6)	106 (83.5)	30.9*
Prior exposure to an IMID, n (%)	139 (90.8)	105 (82.7)	24.3*	115 (43.9)	105 (82.7)	87.9*
Prior exposure to lenalidomide	136 (88.9)	92 (72.4)	42.6*	110 (42.0)	92 (72.4)	64.7*
Prior SCT, n (%)	73 (47.7)	53 (41.7)	12.1*	52 (19.8)	53 (41.7)	48.8*
Refractory status to PIs,[h] n (%)	75 (49.0)	68 (53.5)	9.1	13 (5.0)	68 (53.5)	126.3*
Refractory status to IMIDs,[h] n (%)	15 (9.8)	28 (22.0)	33.9*	18 (6.9)	28 (22.0)	44.2*
Refractory status to lenalidomide,[h] n (%)	13 (8.5)	11 (8.7)	0.6	13 (5.0)	11 (8.7)	14.7*
Refractory to last therapy,[i] n (%)	94 (61.4)	85 (66.9)	11.5*	167 (63.7)	85 (66.9)	6.7

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and the VRd cohort ($56,898; std. diff.: 64.0%); a similar pattern of results was observed for MM-related health care costs among the unweighted cohorts during the baseline period.

After IPTW was applied, the distribution of demographic and clinical characteristics became similar across cohorts (Supplementary Tables 5 and 6). Key confounders that remained imbalanced and were included in the multivariable models for adjustment are listed in the notes of Figures 1-4 and Supplementary Figures 3-8.

HEALTH CARE RESOURCE UTILIZATION

IRd vs KRd. In the post-IPTW comparison of IRd vs KRd (Figure 1), the mean rate of MM-related OP visits PPM was significantly lower for IRd (1.92 vs 4.82; IRR: 0.40, 95% CI = 0.33-0.49; P < 0.0001), which was driven by an absence of OP visits for MM-treatment administration among the IRd cohort compared with a mean rate of 3.03 visits PPM for the KRd cohort. Across all other components of MM-related HCRU, no significant differences were observed between the 2 cohorts.

VRd vs KRd. In the post-IPTW comparison of VRd vs KRd (Figure 2), the mean rate of MM-related OP visits PPM was significantly lower for VRd (3.57 vs 4.84; IRR: 0.74, 95% CI = 0.60-0.91; P = 0.0041), which reflected a lower monthly rate of OP visits for MM-treatment administration with VRd vs KRd (1.61 vs 2.62; IRR: 0.62, 95% CI = 0.49-0.78; P < 0.0001). There were no significant differences between cohorts across other components of MM-related HCRU.

IRd vs VRd. In the post-IPTW comparison of IRd vs VRd, monthly HCRU rates were similar between cohorts with the exception of the MM-related OP visit rate, which was significantly lower in the IRd cohort (Supplementary Figure 7).

Results of pairwise comparisons of all-cause HCRU were consistent with MM-related HCRU. Details can be found in the Supplementary Materials.

TABLE 1 Baseline Characteristics of Patients With RRMM in the Original Sample: IRd vs KRd and VRd vs KRd (*continued*)

	IRd (N = 153)	KRd (N = 127)	Std Diff (%)[a]	VRd (N = 262)	KRd (N = 127)	Std Diff (%)[a]
Time from MM diagnosis to LOT initiation, months						
Mean ± SD	17.3 ± 10.8	13.0 ± 9.2	42.9*	11.3 ± 10.0	13.0 ± 9.2	17.7*
Median (IQR)	14.0 (9.6-23.6)	10.5 (7.6-16.0)	—	8.2 (4.8-14.5)	10.5 (7.6-16.0)	—
Total MM-related health care costs during 6-month baseline period, 2020 USD[f]						
Mean ± SD	115,980 ± 83,404	136,151 ± 95,313	22.5*	77,847 ± 75,619	136,151 ± 95,313	67.8*
Median (IQR)	100,662 (66,524-152,594)	118,485 (70,129-196,160)	—	56,898 (12,991-114 134)	118,485 (70,129-196,160)	—
Total all-cause health care costs during 6-month baseline period, 2020 USD[f]						
Mean ± SD	126,443 ± 85,936	154,048 ± 99,643	29.7*	95,650 ± 81,841	154,048 ± 99,643	64.0*
Median (IQR)	108,984 (71,699-163,348)	131,748 (85,284-213,572)	—	73,819 (29,553-140,985)	131,748 (85,284-213,572)	—

[a]*For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of the comparator and reference cohorts by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs. For dichotomous variables, the standardized difference was calculated using the following equation where P is the respective proportion of participants in each treatment cohort:* $(P_{comparator}-P_{reference})/\sqrt{[(P_{comparator}*(1-P_{comparator}) + P_{reference}*(1-P_{reference}))/2]}$. *Standardized differences ≥10% (as denoted by *) indicated imbalance.*

[b]*The index date was defined as the date of initiation of Rd-backbone triplet therapy in LOT2 or later. For enrollees who were aged older than 85 years, their year of birth in the IQVIA data had been programmatically reset to the year that would return the proxy age of 85 years.*

[c]*Self-insured (also known as "self-funded") refers to a plan in which the employer assumes the financial risk for providing health care benefits to employees.*

[d]*Other payer types include State Children's Health Insurance Plan, Medicaid, and Pharmacy Benefit Only.*

[e]*Multiple responses were allowed, so counts and percentages may not sum to the total N or 100%.*

[f]*Evaluated during the 6-month baseline period prior to the index date.*

[g]*Patients' frailty status is determined by the cumulated score of age and Charlson comorbidity index (i.e., cumulated score 0 = fit, 1 = intermediate, ≥2 = frail). Patient age score (≤75 years = 0 score, 76-80 years = 1 score, ≥81 years = 2 scores). Charlson comorbidity index score (≤1 = 0 score, ≥2 = 1 score).*

[h]*Refractory status to PIs, IMIDs and/or lenalidomide is defined as (1) duration of the PI, IMID, or lenalidomide within an LOT is up to 60 days and the PI/IMID/lenalidomide is not in the next LOT, or (2) the treatment-free interval between the PI/IMID/lenalidomide-containing LOT and the subsequent LOT is up to 60 days and PI/IMID/lenalidomide is not in the subsequent LOT.*

[i]*Refractory to last therapy was defined as a treatment-free interval from the end of previous LOT to initiation of index regimen of ≤60 days.*

CRAB = calcium (elevated) or hypercalcemia, renal insufficiency/impairment, anemia, bone lesions/bone disease/skeletal related events; IMID = immunomodulatory drugs; IRd = ixazomib and lenalidomide, with or without dexamethasone; KRd = carfilzomib and lenalidomide, with or without dexamethasone; LOT = line of therapy; MM = multiple myeloma; PI = proteasome inhibitors; RRMM = relapse/refractory multiple myeloma; SCT = stem cell transplant; Std Diff = standardized difference; USD = United States dollar; VRd = bortezomib and lenalidomide, with or without dexamethasone.

HEALTH CARE COSTS

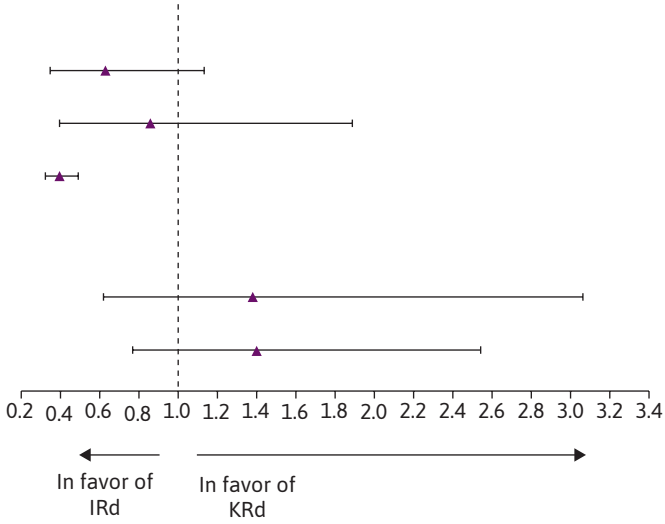
IRd vs KRd. In the post-IPTW comparison of MM-related health care costs for IRd vs KRd, IRd was associated with significantly lower OP costs compared with KRd (mean difference PPPM: –$3,428, 95% CI = –$5,088 to –$2,322; P < 0.001) (Figure 3), which reduced its total medical costs (–$3,813, 95% CI = –$5,406 to –$2,220; P < 0.001), resulting in total MM-related health care cost savings with IRd vs KRd (–$5,813, 95% CI = –$9,295 to –$2,332; P = 0.001). No significant difference in pharmacy and OP treatment administration costs was observed between IRd and KRd (mean difference PPPM: –$2,276, 95% CI = –$4,744 to $192; P = 0.071).

VRd vs KRd. In the post-IPTW comparison of MM-related health care costs for VRd vs KRd, OP costs were significantly lower with VRd than KRd (mean difference PPPM: –$3,543, 95% CI = –$ 5,793 to –$1,663; P < 0.001) (Figure 4), thereby reducing its total medical costs (–$3,997, 95% CI = –$6,548 to –$1,446; P = 0.002). These medical costs savings with VRd, combined with its lower costs for pharmacy and OP treatment administration (mean difference PPPM: –$7,839, 95% CI = –$9,919 to –$5,760; P < 0.001), resulted in total MM-related health care cost savings for VRd vs KRd (–$12,357, 95% CI = –$16,538 to –$8,175; P < 0.001).

IRd vs VRd. The results of the post-IPTW cost comparison among IRd vs VRd cohorts are shown in Supplementary Figure 8. Significant MM-related total medical cost savings were observed with IRd vs VRd (mean difference PPPM: –$1,752, 95% CI = –$3,313 to –$191; P = 0.028). Because IRd was also associated with increased pharmacy and OP treatment

FIGURE 1 Comparisons of MM-Related HCRU Among Patients With RRMM in the Post-IPTW Sample: IRd vs KRd

MM-related HCRU	Rate (per patient-month)[a] IRd	KRd	IRR (95% CI)[b]	*P* value
Hospitalizations	0.02	0.04	0.63 (0.35-1.13)	0.1238
Hospitalization days	0.20	0.23	0.86 (0.40-1.89)	0.7151
OP visits[c]	1.92	4.82	0.40 (0.33-0.49)	**<0.0001**
OP visits for MM treatment administration[d]	—	3.03	—	—
ED visits	0.03	0.02	1.38 (0.62-3.07)	0.4283
Other visits[e]	0.32	0.23	1.40 (0.77-2.54)	0.2676



[a]*Rate of HCRU was calculated by dividing the total number of health care encounters during the LOT by the total patient-months of the LOT and was reported on a patient-month basis.*

[b]*IRRs and associated 95% CIs and P values (bold text denotes statistical significance, P<0.05) were estimated using GLM with a Poisson distribution and robust sandwich estimators, weighted by stabilized IPTW weights and adjusted for baseline covariates. The IPTW model adjusted for the following baseline characteristics: age at index date, sex, geographic region, insurance payer type, index year, CRAB symptoms, Charlson comorbidity index, any MM-related comorbidities, line of therapy number, prior exposure to PI, prior exposure to IMID, prior exposure to lenalidomide, prior stem cell transplant, refractory status to PI, refractory status to IMID, refractory status to last therapy, all-cause, and MM-related total cost. The doubly robust model adjusted for the following baseline characteristics: insurance plan type, index year, refractory status to lenalidomide, CRAB symptoms, MM-related comorbidities, time from MM diagnosis to LOT initiation, time from discontinuation of previous LOT to initiation of LOT, and time from initiation of frontline therapy to first relapse.*

[c]*MM-related OP visits included visits for MM-treatment administration as well as visits not related to MM-treatment administration. All-cause OP visits included visits due to any cause, inclusive of MM-related OP visits.*

[d]*Defined as MM-related OP encounters with a procedure code for MM-treatment administrations.*

[e]*Other visits included ambulatory surgical center, home care, and skilled nursing facility visits.*

CRAB = calcium (elevated) or hypercalcemia, renal insufficiency/impairment, anemia, bone lesions/bone disease/skeletal related events; ED = emergency department; GLM = generalized linear model; HCRU = health care resource utilization; IPTW = inverse probability of treatment weighting; IRd = ixazomib combined with lenalidomide-dexamethasone; IRR = incidence rate ratio; KRd = carfilzomib combined with lenalidomide-dexamethasone; LOT = line of therapy; MM = multiple myeloma; OP = outpatient; RRMM = relapsed/refractory multiple myeloma.

administration costs relative to VRd (mean difference PPPM: $7,106, 95% CI = $5,687-$8,525; P < 0.001), total MM-related health care costs were higher for IRd vs VRd (mean difference PPPM: $5,754, 95% CI = $3,223-$8,285; P < 0.001).

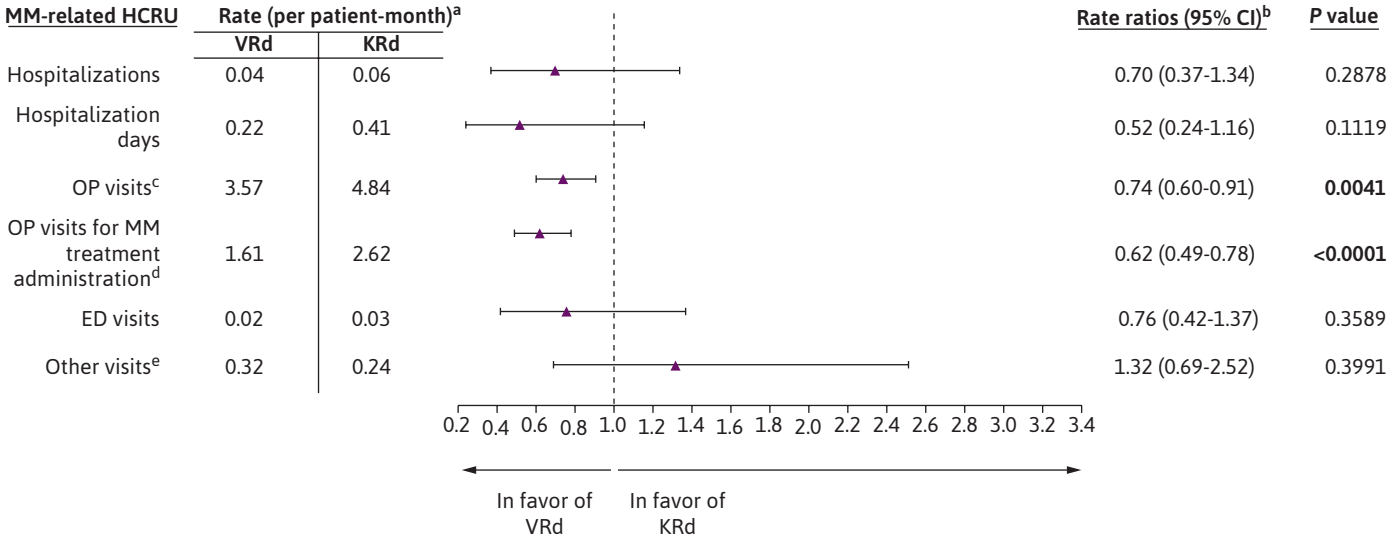
The comparison of all-cause health care costs among each pairwise comparison yielded similar results as MM-related health care costs (Supplementary Materials).

Discussion

This study compared HCRU and health care costs among patients with RRMM treated with IRd, VRd, and KRd in LOT2 or later among a commercially insured US population. Patients initiated on IRd and VRd had significantly lower medical costs for OP services relative to those initiated on KRd, even after excluding OP costs related to MM-treatment administration. Lower medical costs contributed to total health care cost savings for IRd and VRd vs KRd. Similarly, IRd was associated with lower medical costs for OP services when compared with VRd, when excluding treatment administration costs. From a US health care payer perspective, these findings suggest that non–drug-related expenses may be an important driver of cost differences among patients with RRMM treated with IRd, VRd, and KRd.

The present findings are relevant given recent upward trends in non–drug-related health care costs among

FIGURE 2 Comparisons of MM-Related HCRU Among Patients With RRMM in the Post-IPTW Sample: VRd vs KRd



[a]*Rate of HCRU was calculated by dividing the total number of health care encounters during the LOT by the total patient-months of the LOT and was reported on a patient-month basis.*

[b]*IRRs and associated 95% CIs and P values (bold text denotes statistical significance, P<0.05) were estimated using GLM with a Poisson distribution and robust sandwich estimators, weighted by stabilized IPTW weights and adjusted for baseline covariates. The IPTW model adjusted for the following baseline characteristics: age at index date, sex, geographic region, insurance payer type, index year, CRAB symptoms, Charlson comorbidity index, any MM-related comorbidities, line of therapy number, and all-cause and MM-related total cost. The doubly robust model adjusted for the following baseline characteristics: age, insurance plan type, index year, refractory status to PIs, refractory status to IMIDs, prior SCT, prior exposure to a PI, prior exposure to an IMID, prior exposure to lenalidomide, line of therapy number, frailty status, MM-related comorbidities, and time from initiation of frontline therapy to first relapse.*

[c]*MM-related OP visits included visits for MM-treatment administration as well as visits not related to MM-treatment administration. All-cause OP visits included visits due to any cause, inclusive of MM-related OP visits.*

[d]*Defined as MM-related OP encounters with a procedure code for MM-treatment administrations.*

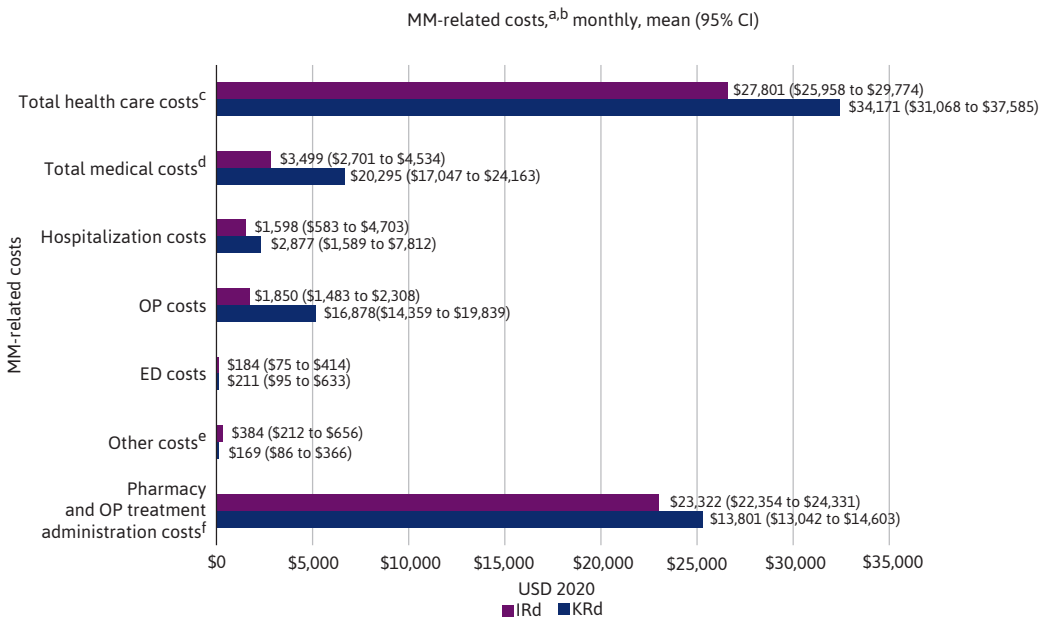
[e]*Other visits included ambulatory surgical center, home care, and skilled nursing facility visits.*

CRAB = calcium (elevated) or hypercalcemia, renal insufficiency/impairment, anemia, bone lesions/bone disease/skeletal related events; ED = emergency department; GLM = generalized linear model; HCRU = health care resource utilization; IRR = incidence rate ratio; IMID = immunomodulatory drugs; IPTW = inverse probability of treatment weighting; KRd = carfilzomib combined with lenalidomide-dexamethasone; LOT = line of therapy; MM = multiple myeloma; OP = outpatient; PI = proteasome inhibitors; RRMM = relapsed/refractory multiple myeloma; SCT = stem cell transplant; VRd = bortezomib combined with lenalidomide-dexamethasone.

patients with MM. Among a large MM population in the United States from 2000 to 2014, one longitudinal cohort study observed an increase in novel therapy use and improved survival, accompanied by a rise in the total health care costs of MM.[4] This increase in total health care costs was primarily driven by non–drug-related costs (eg, OP services and inpatient admissions), whereas the contribution of drug-related costs has remained relatively stable despite new novel therapies coming to market.[4,6] Evidently, this trend might reflect the survival benefits of novel therapies, as patients who live longer with MM are also more likely to develop complications and comorbidities that require medical care.[4] Nonetheless, it is critical to identify novel therapeutic options that might curb these rising medical costs. Lenalidomide became available in a generic form in the United States on March 7, 2022, which will likely reduce its costs considerably, making it more accessible for patients with RRMM.[30] In light of these developments, the cost impact of different PI-based Rd-backbone regimens observed in the present study could help to guide economic decision-making and inform treatment recommendations.

Prior to the present study, only one real-world study from Germany had attempted to compare HCRU and costs among patients with RRMM treated with I-, K-, and V-containing regimens in LOT2 and later.[31] However, this study did not adjust for confounding factors. The distinctive

FIGURE 3 Comparisons of MM-Related Health Care Costs Among Patients With RRMM in the Post-IPTW Sample: IRd vs KRd



Cost difference (95% CI)[a,b]	*P* value
–$6,371 (–$9,994 to –$2,747)	**<0.001**
–$16,796 (–$20,307 to –$13,285)	<0.001*
–$1,279 (–$5,551 to $1,048)	0.165
–$15,028 (–$17,805 to –$12,251)	**<0.001**
–$27 (–$320 to $153)	0.596
$214 (–$35 to $490)	0.102
$9,521 ($8,266 to $10,777)	**<0.001**

[a]*Mean differences and associated 95% CI and P values (bold text denotes statistical significance, P<0.05) for all-cause and MM-related total costs and total medical costs, all-cause pharmacy costs, all-cause OP costs, and MM-related pharmacy and OP treatment administration costs were calculated using a GLM with a γ distribution and a log link, weighted by stabilized IPTW weights. Mean differences for other cost components were calculated using a 2-part model weighted by stabilized IPTW weights. 95% CIs and P values were calculated using a nonparametric bootstrap procedure (n=499).*

[b]*The IPTW model adjusted for the following baseline characteristics: age at index date, sex, geographic region, insurance payer type, index year, CRAB symptoms, Charlson comorbidity index, any MM-related comorbidities, line of therapy number, prior exposure to PI, prior exposure to IMID, prior exposure to lenalidomide, prior stem cell transplant, refractory status to PI, refractory status to IMID, refractory status to last therapy, and all-cause and MM-related total cost. The doubly robust model adjusted for the following baseline characteristics: insurance plan type, index year, refractory status to lenalidomide, CRAB symptoms, MM-related comorbidities, time from MM diagnosis to LOT initiation, time from discontinuation of previous LOT to initiation of LOT, and time from initiation of frontline therapy to first relapse.*

[c]*Total MM-related health care costs were the sum of total medical costs + pharmacy and OP treatment administration costs.*

[d]*Total medical costs included hospitalizations costs, OP costs, ED costs, and other costs.*

[e]*Other costs included costs from ambulatory surgical center, home care, and skilled nursing facility visits.*

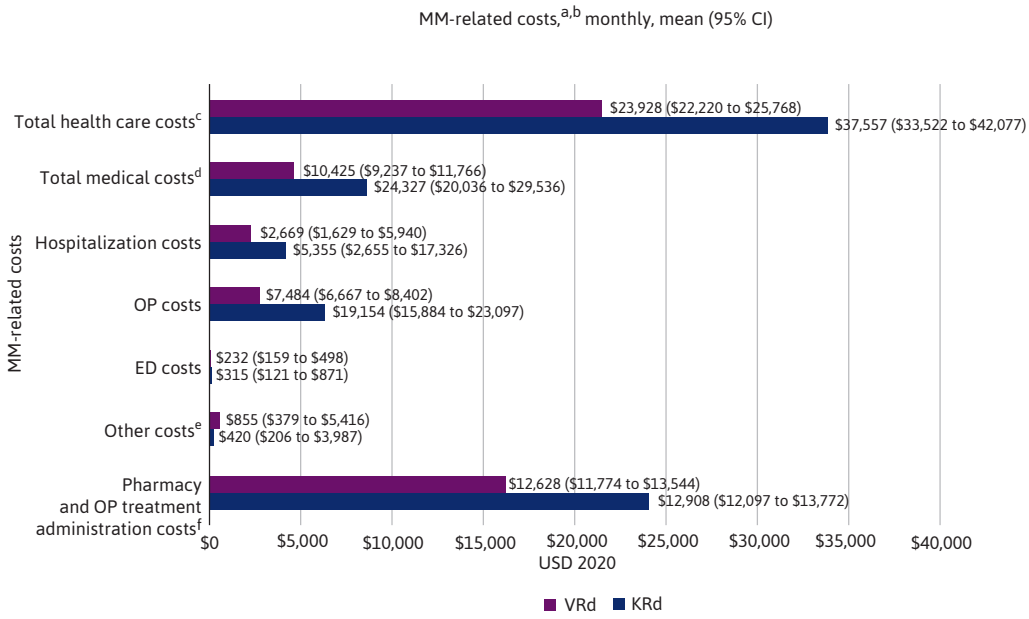
[f]*For MM-related health care costs, MM-treatment administration costs were excluded from OP costs and instead summed together with pharmacy costs. This was done to reflect the costs associated with MM treatment while also accounting for the different billing practices across PIs due to varied routes of administration.*

CRAB=calcium (elevated) or hypercalcemia, renal insufficiency/impairment, anemia, bone lesions/bone disease/skeletal related events; ED=emergency department; GLM=generalized linear model; IMID=immunomodulatory drugs; IPTW=inverse probability of treatment weighting; IRd=ixazomib combined with lenalidomide-dexamethasone; KRd=carfilzomib combined with lenalidomide-dexamethasone; LOT=line of therapy; MM=multiple myeloma; OP=outpatient; PI=proteasome inhibitors; SCT=stem cell transplant; USD=United States dollar.

features of the German health care system further limit the generalizability of these study findings to the US population. Additionally, some prior studies have relied on cost modeling approaches to estimate the economic outcomes associated with different PI-based RRMM regimens.[32–34] A caveat is that the inputs used in these studies were selected at the discretion of the modeler and may have required assumptions that do not reflect real-world practice. The present study addresses these key limitations by sampling from a representative, commercially insured US population, while controlling for potential sources of confounding that might have biased the study results.

A notable aspect of the present study was its use of IQVIA PharMetrics Plus adjudicated claims US data. This database includes patients enrolled in Medicare Advantage plans (between 4% and 20% per cohort) (Table 1) in addition to the

FIGURE 4 Comparisons of MM-Related Health Care Costs Among Patients With RRMM in the Post-IPTW Sample: VRd vs KRd



Cost difference (95% CI)[a,b]	*P* value
–$13,629 (–$18,243 to –$9,014)	**<0.001**
–$13,902 (–$18,893 to –$8,911)	**<0.001**
–$2,686 (–$13,714 to $883)	0.094
–$11,670 (–$15,381 to –$7,958)	**<0.001**
–$83 (–$579 to $179)	0.569
$435 (–$1,709 to $3,786)	0.592
–$280 (–$1,352 to $792)	0.609

[a]*Mean differences and associated 95% CI and P values (bold text denotes statistical significance, P<0.05) for all-cause and MM-related total costs and total medical costs, all-cause pharmacy costs, all-cause OP costs, and MM-related pharmacy and OP treatment administration costs were calculated using a GLM with a γ distribution and a log link, weighted by stabilized IPTW weights. Mean differences for other cost components were calculated using a two-part model weighted by stabilized IPTW weights. 95% CIs and P values were calculated using a nonparametric bootstrap procedure (n=499).*

[b]*The IPTW model adjusted for the following baseline characteristics: age at index date, sex, geographic region, insurance payer type, index year, CRAB symptoms, Charlson comorbidity index, any MM-related comorbidities, line of therapy number, all-cause, and MM-related total cost. The doubly robust model adjusted for the following baseline characteristics: age, insurance plan type, index year, refractory status to PIs, refractory status to IMIDs, prior SCT, prior exposure to a PI, prior exposure to an IMID, prior exposure to lenalidomide, line of therapy number, frailty status, MM-related comorbidities, time from initiation of frontline therapy to first relapse.*

[c]*Total MM-related health care costs were the sum of total medical costs + pharmacy and OP treatment administration costs.*

[d]*Total medical costs included hospitalizations costs, OP costs, ED costs, and other costs.*

[e]*Other costs included costs from ambulatory surgical center, home care, and skilled nursing facility visits.*

[f]*For MM-related health care costs, MM-treatment administration costs were excluded from OP costs and instead summed together with pharmacy costs. This was done to reflect the costs associated with MM treatment while also accounting for the different billing practices across PIs due to varied routes of administration.*

CRAB=calcium (elevated) or hypercalcemia, renal insufficiency/impairment, anemia, bone lesions/bone disease/skeletal related events; ED=emergency department; GLM=generalized linear model; IMID=immunomodulatory drugs; IPTW=inverse probability of treatment weighting; KRd=carfilzomib combined with lenalidomide-dexamethasone; LOT=line of therapy; MM=multiple myeloma; OP=outpatient; PI=proteasome inhibitors; SCT=stem cell transplant; USD=United States dollar; VRd=bortezomib combined with lenalidomide-dexamethasone.

aged-less-than-65 years, commercially insured population in the United States, which allowed our study population to include the elderly so that the results can be generalized to a real-world population. This generalizability of our study population is particularly salient given that more than 50% of patients with RRMM engaged in routine care, including patients of advanced age, are underrepresented in clinical trials of MM treatments.[21] Thus, the present study builds upon a growing body of evidence beyond the clinical trial setting that more accurately reflects the treatment benefits in routine clinical practice and captures the economic impact of IRd and VRd vs KRd among real-world patients with RRMM.

Medical cost savings associated with IRd and VRd vs KRd in our study may at least partly reflect differences in the clinical benefits associated with these regimens, especially in the non–clinical trial, real-world practice setting. Notably, a large US-representative EHR study observed improved treatment outcomes among patients with RRMM initiated on IRd and VRd in LOT2 or later relative to those initiated on KRd, including a longer median duration of treatment

(DOT) and longer time to next treatment.[21] These findings are in turn consistent with the findings obtained in recent meta-analyses of clinical trial data, which demonstrate the efficacy of PI-containing Rd-backbone triplet regimens.[35-37] Additionally, prior evidence suggests that IRd and VRd may also have a more tolerable safety profile than KRd,[12,13,38] which could translate into lower costs related to adverse event management.[32,33] Given that the safety profiles and clinical benefits of these regimens appear to differ in real-world settings relative to clinical trials,[21,39] further studies are needed to clarify the relationship between these outcomes and medical costs among patients with RRMM treated with PI-based Rd-backbone regimens in routine clinical practice.

LIMITATIONS

The present claims-based study may have been subject to data omissions and misspecification of diagnosis, procedure, and medication codes, potentially resulting in misclassification of patient cohorts and endpoints of interest. For instance, physicians may have assigned MM codes at patients' visits irrespective of whether the encounter was related to MM or to another cause; consequently, all-cause encounters might have been misclassified as MM-related. Furthermore, the 3-month washout period used in the present study enabled us to identify incident cases with a reasonable degree of certainty while retaining sufficient sample size for our analysis. However, because providers often adopt a watch and wait approach for early stage MM, some identified patients might not have been true incident cases. Relatedly, claims databases lack certain information relevant to treatment decision-making and outcomes in MM (eg, disease stage, performance score, cytogenetic risk status, and laboratory results), which could impact cost. Additionally, other potential confounders, such as race and ethnicity, were not available for adjustment. Moreover, RRMM was defined based on initiation of LOT 2 instead of diagnosis of RR disease; thus, the algorithm may not reflect patients' true refractory status. Of note, the PI therapies investigated in our study are now recommended in the 1L setting, including in certain circumstances and maintenance therapy, which might have an impact on the use of these therapies in the RRMM routine care setting.[40] That said, more than 70% of patients in the current study had prior exposure to any PI, suggesting retreatment with PI-based regimens is a viable option for management of RRMM. Still, it remains unclear how using PIs in earlier lines could have impacted treatment outcomes in later lines. Because some patients might have received steroid-sparing regimens,[20] we also included those on doublet therapy, thereby increasing our sample size and making it more representative of the real-world population of patients on PI-containing RRMM regimens. Nevertheless, because 455 out of 542 included LOTs were confirmed to be true triplets, we would expect the results to be similar had we restricted the analysis to this population. Taken together, the results of comparative analyses may have been biased due to residual and/or unmeasured confounding. Furthermore, it was not possible to assess certain effectiveness outcomes owing to the lack of availability of key elements in claims databases. For instance, claims data only provide information on treatment administration (eg, OP clinic visits), days of supply, and pharmacy dispensing. This information was sufficient for us to construct a robust LOT sequence based on the LOT algorithm evaluated in other studies.[21-23] However, we were unable to reliably estimate DOT and time to next treatment, as this would require the date of death as well as the actual start and end dates of treatment, which are not available in claims data; nonetheless, the observed time spent on therapy reported among our original sample, which was derived from the date of claims and pharmacy dispensing, could be considered a proxy for DOT. Because the focus of this research was limited to costs from a payer perspective, the present study did not assess copay or out-of-pocket costs, which may represent a barrier to accessing therapies from the patient perspective.[5] Finally, although prior studies have reported high indirect costs associated with injectable treatments among patients with RRMM and their caregivers,[41] we were unable to capture indirect costs in the present study.

Conclusions

The introduction of PI-based Rd triplet regimens have transformed the management of RRMM. Although PI-Rd triplet regimens are commonly used and provide longer disease-free periods compared with doublet regimens,[14-17] information regarding the associated health care costs of these regimens has been limited. From the US health care payer perspective, this real-world study is one of the first to provide comparative data on the HCRU/costs of PI-Rd triplet regimens. The results suggest that medical costs are an important driver of the economic impact of PI-based Rd-backbone triplet RRMM regimens. In particular, patients treated with IRd and VRd have significant medical cost savings when compared with KRd, driven primarily by lower OP expenses excluding treatment administration costs. The impact of PI-Rd regimens on HCRU/costs observed in this study, combined with prior comparative effectiveness data demonstrating better outcomes associated with IRd and VRd relative to KRd,[21] may guide economic

decision-making and inform treatment recommendations for patients with MM in the real-world.

DISCLOSURES

This study and article were supported by Takeda Development Center Americas, Inc. Dr Sanchez has no conflicts to declare. Dr Chari has the following relationships: Research Support/Principal Investigator: Amgen, Array Biopharma, Celgene, Glaxo Smith Klein, Janssen, Millenium/Takeda, Novartis Pharmaceuticals, Oncoceutics, Pharmacyclics, Seattle Genetics; Consultant: Amgen, Bristol-Myers Squibb, Celgene, Millenium/Takeda, Janssen, Karyopharm; Scientific Advisory Board: Amgen, Celgene, Millenium/Takeda, Janssen, Karyopharm, Sanofi, Seattle Genetics. Drs Cherepanov, Huang, Dabora, and Noga are current employees of Takeda, while Drs Stull and Young are ex-employees of Takeda; Drs Cherepanov and Huang also own stocks in Takeda. Dr DerSarkissian, Ms Cheng, Ms Zhang, Mr Banatwala, and Dr Duh are employees of Analysis Group, Inc. (AG), a consulting firm that received funding from Takeda to conduct this study. Ms Pi was an employee of AG at the time of the study. Dr Ailawadhi has the following relationships to declare: Research Support and Consulting for BMS, GSK, and Janssen; Research Support from AbbVie, Arch Oncology, Cellectar, Medimmune, Pharmacyclics, and Xencor; Consulting for Beigene, Oncopeptides, Regeneron, Sanofi, and Takeda.

ACKNOWLEDGMENTS

Medical writing and editorial assistance was provided by Mona Lisa Chanda, PhD, an employee of Analysis Group, Inc. Support for this assistance was provided by Takeda Development Center Americas, Inc.

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