Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: https://www.tandfonline.com/loi/ierr20

Real-world outcomes and factors impacting treatment choice in relapsed and/or refractory multiple myeloma (RRMM): a comparison of VRd, KRd, and IRd

Ajai Chari, Paul G. Richardson, Dorothy Romanus, Meletios A. Dimopoulos, Pieter Sonneveld, Evangelos Terpos, Roman Hajek, Aditya Raju, Antonio Palumbo, Lauren E. Cain, Marlo Blazer, Hui Huang, Eileen Farrelly & Sikander Ailawadhi

To cite this article: Ajai Chari, Paul G. Richardson, Dorothy Romanus, Meletios A. Dimopoulos, Pieter Sonneveld, Evangelos Terpos, Roman Hajek, Aditya Raju, Antonio Palumbo, Lauren E. Cain, Marlo Blazer, Hui Huang, Eileen Farrelly & Sikander Ailawadhi (2020) Real-world outcomes and factors impacting treatment choice in relapsed and/or refractory multiple myeloma (RRMM): a comparison of VRd, KRd, and IRd, Expert Review of Hematology, 13:4, 421-433, DOI: 10.1080/17474086.2020.1729734

To link to this article: https://doi.org/10.1080/17474086.2020.1729734

EXPERT REVIEW OF HEMATOLOGY
2020, VOL. 13, NO. 4, 421–433
https://doi.org/10.1080/17474086.2020.1729734

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Real-world outcomes and factors impacting treatment choice in relapsed and/or refractory multiple myeloma (RRMM): a comparison of VRd, KRd, and IRd

Ajai Chari [a], Paul G. Richardson[b], Dorothy Romanus[c], Meletios A. Dimopoulos [d], Pieter Sonneveld [e], Evangelos Terpos [d], Roman Hajek[f], Aditya Raju[g], Antonio Palumbo[c], Lauren E. Cain[c], Marlo Blazer[g], Hui Huang[c], Eileen Farrelly[g] and Sikander Ailawadhi[h]

[a]Department of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [b]Jerome Lipper Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [c]Global Outcomes Research, Millennium Pharmaceuticals, Inc., A Wholly Owned Subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA; [d]Hematology & Medical Oncology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece; [e]Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [f]University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [g]Scientific Consulting, Xcenda, Palm Harbor, FL, USA; [h]Division of Hematology/Oncology, Department of Medicine, Mayo Clinic, Jacksonville, FL, United States

ABSTRACT

Lack of head-to-head trials highlights a need for comparative real-world evidence of proteasome inhibitors plus Rd.

Methods: In this retrospective, US population-representative EHR study of RRMM patients initiating IRd, KRd, or VRd in line of therapy (LOT) ≥2 between 1/2014 and 9/30/2018, 664 patients were treated in LOT ≥2 with: IRd, n = 168; KRd, n = 208; VRd, n = 357. Median age was 71/65/71 years; 67%/70%/75% had a frailty$_{modified}$ score of intermediate/frail; 20%/28%/13% had high cytogenetic risk in I-/K-/V-Rd groups. Risk of PI-triplet discontinuation was lower for I- vs. K-Rd (HR: 0.71) and I- vs. V-Rd (HR: 0.85); unadjusted, median TTNTs (months): 12.7/8.6/14.2 (LOT ≥2) and 16.8/9.5/14.6 (LOT 2–3) (I-/K-/V-Rd). Adjusted TTNT was comparable between I-/K-/V-Rd in LOT ≥2 with a TTNT benefit among intermediate/frail patients for I- (HR: 0.70; P=0.04) and V- (HR: 0.73; P<0.05) vs. K-Rd. I/K/V-Rd triplets were comparable in TTNT overall, but IRd and VRd were associated with longer TTNT in intermediate/frail patients than KRd. The results suggest a trial-efficacy/real-world-effectiveness gap, especially for KRd, underlining the limited generalizability of trial results where >50% of patients are excluded. Individualized treatment based on patient characteristics, such as frailty status, is especially pertinent in an elderly RRMM population.

ARTICLE HISTORY
Received 17 January 2020
Accepted 11 February 2020

KEYWORDS
Bortezomib; carfilzomib; ixazomib; PI-triplet therapy; proteasome-inhibitor-triplet therapy; real world; relapsed refractory multiple myeloma; RRMM

1. Introduction

Multiple myeloma (MM) accounts for 1.8% of all cancers in the United States (US) and is the second most common hematologic malignancy, with an estimated 32,000 new cases and 13,000 deaths in 2019 [1]. MM is more common in the elderly [1–4]. In the US, the median age at diagnosis is 69 years, with the majority of individuals diagnosed between the ages of 65 and 74 years [1], and 62% patients are treated in the community setting vs. in academic centers, where younger, less comorbid, clinical trial-eligible patients are more likely to be seen [5].

The introduction of novel classes of agents with increased efficacy, including proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs), changed the treatment paradigm and has increased overall survival (OS) in MM [6,7,]. While bortezomib (V) plus lenalidomide/dexamethasone (Rd) has been compared vs. Rd in a large phase 3 study in frontline treatment (SWOG S0777), in the relapsed/refractory multiple myeloma (RRMM) setting, only single-arm phase 2 data have been published, which reported a median progression-free survival (PFS) of 9.5 months [8,9,]. The newer PI-triplet combinations with Rd, i.e. with ixazomib (IRd) and carfilzomib (KRd), have both demonstrated superior efficacy vs. the Rd doublet among patients with RRMM who have had 1 to 3 prior lines of therapy [10,11,]. In the phase 3 ASPIRE trial, the addition of carfilzomib (K) to Rd (KRd) significantly increased PFS vs. Rd alone (26.3 months vs. 17.6 months; hazard ratio [HR]: 0.69; P = 0.0001) [10]. Likewise, the addition of ixazomib (I) to Rd (IRd) in the TOURMALINE-MM1 phase 3 study increased the PFS to 20.6 months vs. 14.7 months for Rd alone (HR: 0.74; P = 0.01) [11]. Notably, the Rd control arm performed differently, with an almost 3-month difference in PFS, between the two phase 3 studies [10,11,], which in part stems from differences in eligibility criteria within these individual trials. The lack of head-to-head trials of the PI-Rd triplet regimens, coupled with differences in the trial populations studied, has led to

CONTACT Sikander Ailawadhi ailawadhi.sikander@mayo.edu Division of Hematology/Oncology, Department of Medicine, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Presented, in part, at the 61st Annual Meeting and Exposition of the American Society of Hematology (ASH); December 7–10, 2019; Orlando, Florida.

Supplemental data for this article can be accessed here.

challenges in comparisons of treatment effects across trials.

Furthermore, the extent to which the efficacy results seen in those trials translate to real-world effectiveness in older adults with RRMM needs further examination to help inform individualized treatment decision-making. Understanding real-world effectiveness is especially relevant in MM since patients are diagnosed at an advanced age that is often associated with organ function decline, which may decrease treatment tolerability and affect the outcomes of therapy. In patients with MM, advanced age and higher comorbidity burden are factors that are under-represented in clinical trials. A recent real-world analysis reported that up to 75% of patients with RRMM engaged in routine care in the US do not meet the eligibility criteria of hallmark clinical trials of approved or recommended regimens in this setting and that 3-year OS was significantly and negatively impacted by the inability to meet eligibility requirements [12]. Greater comorbidities and poorer performance status result in worse treatment outcomes [13]. Evidence from a pooled analysis of prospective trials demonstrates that MM patients with an intermediate or frail status, based on a geriatric assessment, had a significantly higher mortality risk compared to those categorized as fit [14]. In addition, the frailty score was predictive of the risk of toxicity independent of standard risk stratification factors, with a significantly higher incidence of non-hematologic toxicity among frail compared to fit patients [14]. Given the complexity in the interpretation of trial data, limited generalizability of trial findings, shorter duration of therapy in real-world use relative to clinical trials, and lack of head-to-head trial comparisons, MM experts have called for real-world effectiveness as a metric to include in routine clinical practice [13].

2. Objectives

We conducted a retrospective, comparative analysis of time to next therapy (TTNT), a proxy for PFS [15–18], in a representative cohort of patients with RRMM treated in routine care with IRd, KRd, or VRd in lines of therapy (LOTs) 2 or greater. Considering the under-representation of older and comorbid patients in clinical trials and the prognostic and predictive importance of frailty status in MM, we also compared real-world TTNT by frailty status (modified using age and comorbidities). Finally, we evaluated patient, disease, and prior treatment characteristics that are independently associated with regimen choice.

3. Methods

3.1. Data source

This was a retrospective cohort study using Optum's de-identified electronic health record (EHR) database; this is a general population-representative dataset with data from over 140,000 providers, 7,000 clinics, and 700 hospitals treating more than 95 million patients across 50 states in the US. To mitigate patient selection bias at the practice level, within each participating hospital, clinic, or provider, data for all patients are captured within the EHR database. Data are certified as deidentified in line with the US Health Insurance Portability and Accountability Act statistical de-identification rules. This study was approved by the Advarra Institutional Review Board.

3.2. Study design and population

Included patients were adults who initiated a triplet regimen containing I, K, or V plus an Rd backbone (i.e. IRd, KRd, or VRd) in LOT ≥2 (index LOT) after 1 January 2014. Patients newly diagnosed with MM were identified using data from the start of the available EHR data during the study period (i.e. from 1 July 2007 through 30 September 2018) and followed longitudinally to identify the index LOT. The index diagnosis date for each patient was defined as the first chronologically occurring MM diagnosis during this period in order to identify newly diagnosed patients.

Other inclusion criteria included initiation of one of the regimens of interest (i.e. IRd or KRd or VRd in LOT ≥2 [index LOT]) and receipt of continuous care in an integrated delivery network for 6 months prior to the MM diagnosis date through at least initiation of index LOT to ensure data completeness. Exclusion criteria included: receipt of a stem-cell transplant (SCT) during the index LOT and evidence of anticancer MM therapy or SCT during the 6-month wash-out period prior to MM diagnosis (i.e. to ensure that the study population consisted of newly diagnosed MM patients [incident cases]). (Appendix Figure 1).

To holistically examine the comparative effectiveness of the index regimens as reflected by their real-world use irrespective of sequencing, we opted to include recurrent use of the index regimens within a patient for the main analysis (e.g. VRd in LOT 2 followed by IRd in LOT 3) rather than restricting to only the first use of the index regimen (e.g. VRd in LOT 2 in the previous example). A sensitivity analysis based on the first use of the index regimen was also conducted (Online Appendix Table 1). Hence, the unit of measure was patient LOT, and the index treatment date for each PI-Rd triplet index LOT of interest was the first date that each triplet was initiated. The 6-month period prior to each index LOT initiation date, termed the baseline period, was used to characterize study patients. The follow-up period for this analysis began with the index LOT initiation date until death, loss to follow-up, or end of the study period (9/30/2018), whichever occurred first.

3.3. Study variables

Baseline demographic and clinical characteristics were assessed via diagnosis codes, lab values, unstructured data, and structured fields within the EHR. Measures of interest included the following: Charlson comorbidity index (CCI) [19], CRAB symptoms (hyperCalcemia [identified via ICD-9/10 code or lab value indicating corrected serum calcium >11 mg/dL], Renal insufficiency [defined as lab value indicating serum creatinine >2 mg/dL or creatinine clearance <40 mL/min], Anemia [identified via ICD-9/10 code or hemoglobin level <10 gm/dL], and Bone lesions [proxied by fracture, radiation to bone, bone-directed surgery, or spinal cord compression])

[20], peripheral neuropathy (PN), International Staging System (ISS) stage, Eastern Cooperative Oncology Group (ECOG) performance status, and SCT status. Cytogenetic risk (high-risk, defined as the presence of del[17p], t[4;14], t[14;16], and/or 1q21 gain) was ascertained using natural language processing of free-text elements to capture relevant information not available in standardized fields. Patients with missing data were categorized separately. A modified frailty score based on Palumbo et al. [14] was employed utilizing age and CCI score only (Online Appendix Table 2). While the frailty score validated by Palumbo et al. consisted of four components (age, CCI, the Katz Activity of Daily Living [ADL], and the Lawton Instrumental Activity of Daily Living [IADL]), the physician-reported ADL and IADL scores were not available within the analytic EHR dataset.

Further, given the age of the studied population and mix of cardiovascular comorbidities that affect treatment choice, an expanded definition of cardiovascular disease was employed [12]. Presence of cardiovascular disease was captured via ICD-9/10 coding for myocardial infarction (MI), angina, coronary artery disease (CAD), arrhythmia, sick sinus syndrome, or heart failure (HF); however, to ensure only severe (i.e. uncontrolled or symptomatic cases) were recorded, identification required 1 inpatient encounter coded as primary or discharge or any two outpatient encounters with primary diagnosis codes that were 60 to 365 days apart, with the first one occurring within 6 months prior to start of the index regimen [12]. Presence of uncontrolled hypertension (HTN) was identified via 1 inpatient or 2 outpatient ICD-9/10 codes for HTN that were 60 to 365 days apart with an accompanying blood pressure measurement ≥160/100 mmHg (corresponding to Common Terminology Criteria for Adverse Events grade ≥3) based on the most recent measurement within 14 days prior to index regimen [12].

The algorithm for LOT determination in the EHR was developed in collaboration with several hematology/oncology specialists to proxy the definition of a LOT within the randomized controlled trials and in accordance with the National Comprehensive Cancer Network Guidelines for treatment of MM [21,22,] (see Online Appendix for more details). Time from MM diagnosis to index LOT (in months) was defined as the time from the MM diagnosis date to the start of the index regimen; time of first relapse was proxied as time from start of LOT 1 to start of LOT 2; treatment-free interval (TFI) (in months) was defined as the time from the end of the previous LOT to the start of the index LOT, with a TFI of ≤60 days categorized as 'refractory to last therapy,' which is associated with more aggressive disease (Appendix Figure 2). Refractory status to any PIs or any IMIDs was defined as follows: duration of therapy of the IMID or PI within an LOT was ≤60 days and the PI/IMID was not in next LOT, or the TFI between LOTs was ≤60 days and the PI or IMID was not in the subsequent LOT [23].

3.4. Outcomes

The primary outcome of interest was TTNT. TTNT (a surrogate measure for PFS in real-world analyses) was defined as the time from the start of the index LOT to initiation of the subsequent line of therapy or death, whichever occurred earlier. Patients were censored if they did not have an event (start of next LOT/death) by the end of study period or date of last EHR activity. We also evaluated duration of therapy (DOT) of the index regimen, which was defined as the time from initiation of the first drug in the index regimen to discontinuation of the last drug in the regimen plus a run-out period or death, whichever occurred earlier. The DOT of the individual agents (i.e. the PI component and lenalidomide) within the index LOT was also evaluated utilizing the initiation date of the agent and the last date administered for the agent plus the run-out period or death. The run-out date for infused/injected drugs was the latest date of administration +30 days; for orally administered drugs, it was the fill date + (days' supply −1)

3.5. Statistical analysis

We compared the balance of baseline characteristics across the three treatment groups (IRd, KRd, and VRd); characteristics by treatment category were presented as counts and percentages for categorical variables and means, standard deviations, medians, and interquartile ranges for continuous variables. As a single patient could be in multiple treatment groups, some correlation is expected because patients may be included in more than one treatment group; however, to adequately account for correlation between observations, statistical differences in baseline characteristics were assessed using generalized estimating equation models. For binary variables, a binomial distribution and log link function were specified; for other categorical variables, a multinomial distribution and cumulative log link were specified; and for continuous variables, ranks were assigned to the observations and compared across treatment groups using a GENMOD model.

Furthermore, we were also interested in evaluating patient, disease, and treatment characteristics that are independently associated with treatment choice. A conditional logistic model (stratified by LOT 2–3 vs. ≥4) was used to assess the associations of covariates with the three treatment groups (IRd, KRd, VRd). Based on clinical input, the following candidate predictor variables were included in the model: modified frailty score (0 [fit], 1–2 [intermediate to frail]), any prior PI exposure, any prior IMID exposure, prior SCT, history of PN, history of cardiovascular disease (CVD)/uncontrolled HTN, symptomatic relapse evaluated based on baseline CRAB symptoms (presence of any of the following: hypercalcemia, renal failure, anemia, bone disease [any, yes vs. no]), cytogenetic risk (high, standard/unknown), ISS stage (I/II, III, unknown), time (in months) from diagnosis to start of index LOT, time of first relapse (in months) (i.e. time from start of LOT1 to start of LOT2), and refractory status to last therapy (TFI of ≤60 days vs. >60 days preceding the index LOT).

We compared TTNT and DOT across the three treatment groups; these were estimated using Kaplan-Meier methods. The risk of initiation of the next LOT or death, whichever occurred first, in the overall cohort receiving one of the index regimens in LOT ≥2 was compared using Cox proportional hazard (PH) models. All survival analyses were stratified by LOT (2–3 vs. ≥4). In addition, we conducted covariate-adjusted multivariate Cox PH analyses of TTNT. The following

variables were included in multivariate models: index regimen type (IRd, KRd, VRd), modified frailty score (0 [fit], 1–2 [intermediate to frail]), ECOG score (0-1, 2-4, unknown), prior PI and/or IMID exposure, prior SCT, history of CVD or uncontrolled HTN, history of PN, or baseline CRAB symptoms (hypercalcemia, renal failure, anemia, bone disease [all, yes vs. no]), cytogenetic risk (high, standard/unknown), ISS stage (I/II, III, unknown), PI/IMID refractory status (PI and/or IMID refractory, refractory to neither), time (months) from diagnosis to start of index LOT, refractory status to last therapy (TFI of ≤60 days vs. >60 days preceding the index LOT), time of first relapse (months) (i.e. time from start of LOT1 to start of LOT2), and year of diagnosis (2007–2011, 2012–2015, 2016–2018). To account for correlation between observations that can occur when a single patient can be in more than one treatment group, between-cluster (patient) variance was computed from robust sandwich estimators for adjusted standard errors in the Cox PH analyses. Use of the standard Cox PH estimation of variance, without robust sandwich estimators, would have increased the chance of type I error and thus the possibility of erroneously claiming a significant finding. In addition, a sensitivity analysis was performed based on first use of the index regimen only (patient-level analysis) and compared to the patient LOT-level analysis. Further, to evaluate the impact on the main results of missing data for prognostic indicators, sensitivity analyses were conducted for adjusted TTNT by including patients with only known values of ECOG PS, ISS stage, and cytogenetic risk. Observations were censored at time of loss to follow-up or end of study period.

Given the known differences in a real-world RRMM population vs. those meeting the strict eligibility criteria within clinical trials [12], we conducted a subgroup analysis in real-world patients treated in earlier LOTs (i.e. LOT 2 or 3) who are more representative of the clinical trial population. We also performed subgroup analyses on the following subgroups of interest: those with modified frailty scores (i.e. intermediate/frail, fit), and those with prior PI exposure. For the latter, we also performed a sensitivity analysis based on exposure to bortezomib in first-line therapy.

4. Results

4.1. Baseline characteristics

Out of 3,009 RRMM patients treated with LOT ≥2 after 1 January 2014, 664 patients initiating IRd, KRd, or VRd in LOT ≥2 were identified, accounting for 733 patient LOTs (IRd, n = 168; KRd, n = 208; VRd, n = 357).

The median age in the KRd group (65 years) was significantly lower than in the IRd and VRd groups (71 years for both; $P < 0.01$). Accordingly, a larger proportion of patients who were <65 years of age received KRd compared with the other triplet groups (50.0% vs. 36.3%, IRd and 31.9%, VRd), and higher percentage of patients (41.7%) in the IRd group were ≥75 years of age than the other triplet groups (22.1%, KRd; 38.1%, VRd; $P < 0.01$). Significant differences by frailty status were similarly noted across the treatment groups ($P < 0.01$), with more patients selected for VRd therapy who were deemed intermediate/frail via the modified frailty score (75.1% vs. 67.3%, IRd and 69.7%, KRd). The age by CCI score distribution across treatment groups utilized in the modified frailty score calculation is detailed in the Online Appendix Table 3.

A larger proportion of all patients selected for KRd vs. IRd or VRd had known high-risk cytogenetics (28.4% vs. 20.2%, IRd and 13.5%, VRd), although cytogenetic data were missing for the majority of patients (Table 1). Further, more patients selected for KRd had symptomatic relapse, as determined by the presence of any CRAB symptoms, than those selected for IRd or VRd (87.5% vs. 71.4%, IRd and 80.4%, VRd; $P < 0.01$ for both). Other notable differences in baseline characteristics for the overall (LOT ≥2) population included more patients treated with VRd who received treatment in LOT 2 (70.3%) followed by KRd (50.0%) and IRd (36.9%); $P < 0.001$, and correspondingly fewer VRd patients were refractory to a previous PI and/or an IMID (13.7% vs. 58.9%, IRd and 80.8%, KRd) or had prior exposure to both a PI and an IMID (31.9% vs. 62.5%, IRd and 69.7%, KRd); $P < 0.001$ for both (Table 1). Among those with exposure to a PI (with or without an IMID) prior to index LOT, 78% (n = 460) had their first exposure to a PI in LOT 1; of these, 96.3% (n = 443) consisted of bortezomib-based therapy.

These differences by regimen type in baseline characteristics (in age, frailty status [i.e. by modified frailty score], and cytogenetics), including a significantly longer time from diagnosis of MM to start of IRd vs. KRd or VRd, were also consistent for the subset of patients receiving one of these PI triplets in earlier LOTs (i.e. in LOTs 2 and 3) (Online Appendix Table 4).

4.2. Factors associated with regimen choice

The multivariate results for patient and disease characteristics that were independently and significantly associated with the index regimen choice among patients receiving IRd, KRd, or VRd in LOT ≥2 are listed in Figure 1 and the remaining non-significant factors evaluated are listed in Supplemental Table 5, Online Appendix.

Our patients with RRMM were more likely to be treated with IRd vs. VRd if they had high-risk cytogenetics (odds ratio [OR]: 1.96; 95% confidence interval [CI]: 1.14, 3.38; $P = 0.0152$) and prior IMID exposure reflecting the use of IRd in later LOTs, which was primarily lenalidomide (OR: 4.34; 95% CI: 2.52, 7.49; $P < 0.0001$). High-risk cytogenetics (OR: 2.41; 95% CI: 1.47, 3.96; $P = 0.0005$) and prior IMID exposure (OR: 2.59; 95% CI: 1.66, 4.05; $P < 0.0001$) also influenced the choice of KRd over VRd. Further, patients were more likely to receive KRd vs. VRd if they had symptomatic relapse (OR: 2.01; 95% CI: 1.11, 3.63; $P = 0.0214$), a history of PN (OR: 2.39; 95% CI: 1.42, 4.01; $P = 0.0010$), relapse after a prior SCT (OR: 1.65; 95% CI: 1.03, 2.63; $P = 0.0382$), or prior exposure to a PI (OR: 7.34; 95% CI: 3.51, 15.34; $P < 0.0001$).

In terms of choice between the two newer PIs, patients were more likely to receive IRd vs. KRd if they had prior IMID exposure (OR: 2.24; 95% CI: 1.18, 4.24; $P = 0.0134$). Conversely, patients were less likely to be treated with IRd vs. KRd if they had a symptomatic relapse (OR: 0.44; 95% CI: 0.23, 0.83; $P = 0.0111$), prior PI exposure (OR: 0.21; 95% CI: 0.10, 0.47; $P = 0.0001$), or relapse after a prior SCT (OR: 0.43; 95% CI: 0.25,

Table 1. Baseline clinical and treatment characteristics by regimen type, index lines of therapy ≥2.

Variable, N (%) except where noted		Regimen type				
		Overall N = 733	IRd N = 168	KRd N = 208	VRd N = 357	*P*-value
Age, median years (IQR)		69 (61, 77)	71 (62, 79)	65 (56, 74	71 (62, 78)	<0.0001
Age group, years	**<65**	279 (38.1)	61 (36.3)	104 (50.0)	114 (31.9)	<0.0001
	65–74	202 (27.6)	37 (22.0)	58 (27.9)	107 (30.0)	
	≥75	252 (34.4)	70 (41.7)	46 (22.1)	136 (38.1)	
CCI score[a]	**0**	224 (30.6)	66 (39.3)	54 (26.0)	104 (29.1)	0.0272
	1	67 (9.1)	15 (8.9)	22 (10.6)	30 (8.4)	
	≥2	442 (60.3)	87 (51.8)	132 (63.5)	223 (62.5)	
ECOG PS	**0–1**	203 (27.7)	53 (31.6)	63 (30.3)	87 (24.4)	0.2090
	2–4	33 (4.5)	7 (4.2)	8 (3.9)	18 (5.0)	
	Unknown	497 (67.8)	108 (64.3)	137 (65.9)	252 (70.6)	
Modified frailty score[b]	**Fit**	207 (28.2)	55 (32.7)	63 (30.3)	89 (24.9)	0.0053
	Intermediate	346 (47.2)	66 (39.3)	115 (55.3)	165 (46.2)	
	Frail	180 (24.6)	47 (28.0)	30 (14.4)	103 (28.9)	
Cytogenetics[c]	**High risk**	141 (19.2)	34 (20.2)	59 (28.4)	48 (13.5)	0.0001
	Standard risk[d]	9 (1.2)	5 (3.0)	2 (1.0)	2 (0.6)	
	Unknown	583 (79.5)	129 (76.8)	147 (70.6)	307 (86.0)	
CRAB symptoms[a,e]	**Any**	589 (80.4)	120 (71.4)	182 (87.5)	287 (80.4)	0.0010
	RI	332 (45.3)	55 (32.7)	94 (45.2)	183 (51.3)	0.0003
	Anemia	509 (69.4)	103 (61.3)	165 (79.3)	241 (67.5)	0.0005
	Hypercalcemia	88 (12.0)	12 (7.1)	33 (15.9)	43 (12.0)	0.0280
	Bone disease	155 (21.2)	30 (17.9)	55 (26.9)	69 (19.3)	0.0603
Comorbidities of interest[a]	**CVD[f] or uncontrolled HTN**	95 (13.0)	21 (12.5)	33 (15.9)	41 (11.5)	0.3400
	Peripheral neuropathy	121 (16.5)	30 (17.9)	49 (23.6)	42 (11.8)	0.0021
ISS stage	**I/II**	155 (21.2)	26 (15.5)	50 (24.0)	79 (22.1)	0.4573(excludes unknown)
	III	47 (6.4)	5 (3.0)	18 (8.7)	24 (6.7)	
	Unknown	531 (72.4)	137 (81.6)	140 (67.3)	254 (71.2)	
Year of diagnosis	**2007–2011**	125 (17.1)	32 (19.1)	35 (16.8)	58 (16.2)	0.6487
	2012–2015	437 (59.6)	100 (59.5)	124 (59.6)	213 (59.7)	
	2016–2018	171 (23.3)	36 (21.4)	49 (23.6)	86 (24.1)	
TREATMENT CHARACTERISTICS						
Index LOT	**2**	417 (56.9)	62 (36.9)	104 (50.0)	251 (70.3)	<0.0001
	3	169 (23.1)	54 (32.1)	46 (22.1)	69 (19.3)	0.0101
	≥4	147 (20.1)	52 (31.0)	58 (27.9)	37 (10.4)	<0.0001
Number of prior LOTs	Mean (SD)	1.8 (1.3)	2.3 (1.5)	2.1 (1.5)	1.5 (0.9)	<0.0001
	Median (range)	1.0 (1, 9)	2.0 (1, 8)	1.5 (1, 9)	1.0 (1, 7)	

(*Continued*)

Table 1. (Continued).

Variable, N (%) except where noted		Regimen type				
		Overall N = 733	IRd N = 168	KRd N = 208	VRd N = 357	*P*-value
Prior exposure to a PI or IMID[g]	**Both IMID and PI**	364 (49.7)	105 (62.5)	145 (69.7)	114 (31.9)	<0.0001
	IMID only	131 (17.9)	39 (23.2)	7 (3.4)	85 (23.8)	<0.0001
	PI only	225 (30.7)	22 (13.1)	53 (25.5)	150 (42.0)	<0.0001
	Neither	13 (1.8)	2 (1.2)	3 (1.4)	8 (2.2)	0.6264
Refractory status to PIs and/or IMIDs	**Both IMID and PI**	91 (12.4)	38 (22.6)	45 (21.6)	8 (2.2)	<0.0001
	IMID only	49 (6.7)	12 (7.1)	10 (4.8)	27 (7.6)	0.4233
	PI only	176 (24.0)	49 (29.2)	113 (54.3)	14 (3.9)	<0.0001
	Neither	417 (56.9)	69 (41.1)	40 (19.2)	308 (86.3)	<0.0001
Refractory to last therapy[h]		584 (79.7)	124 (73.8)	179 (86.1)	281 (78.7)	0.0072
Prior SCT		181 (24.7)	40 (23.8)	72 (34.6)	69 (19.3)	0.0006
Time (months) from Initiation of frontline therapy to first relapse, median (IQR)[i]		11.2 (5.7, 20.5)	13.8 (7.8, 24.9)	10.1 (5.3, 17.2)	10.5 (5.5, 19.6)	0.0007
Time (months) from diagnosis to index LOT, median (IQR)		21.7 (10.1, 44.7)	33.6 (17.0, 55.2)	19.8 (9.6, 42.2)	18.4 (8.5, 35.2)	<0.0001

[a]Baseline presence is relative to 6 months prior to initiation of index LOT.
[b]Adapted from Palumbo et al. (*Blood*. 2015;125(13):2068–2074) and includes age and CCI score only, as IADL and ADL were not available in the EHR database.
[c]High-risk cytogenetics were defined as presence of del[17p], t[4;14], t[14;16], and/or 1q21 gain.
[d]Cytogenetic/FISH test done and high risk not explicitly mentioned.
[e]CRAB symptoms were not mutually exclusive, as patients could have ≥1 comorbidity.
[f]CVD includes MI, angina, CAD, arrhythmia, sick sinus syndrome, ischemia, and HF.
[g]Greater than 96% of prior IMID use across all treatment groups was lenalidomide.
[h]Defined as a TFI from the end of previous LOT to initiation of index regimen of ≤60 days.
[i]Defined as time from initiation of LOT1 to initiation of LOT2.
Key: ADL – activities of daily living; CCI – Charlson comorbidity index; CAD – coronary artery disease; CVD – cardiovascular disease; ECOG – Eastern Cooperative Oncology Group; FISH – fluorescence *in situ* hybridization; IADL – instrumental activities of daily living; IMID – immunomodulatory drug; HF – heart failure; HTN – hypertension; IQR – interquartile range; IRd – ixazomib, lenalidomide, dexamethasone; ISS – International Staging System; KRd – carfilzomib, lenalidomide, dexamethasone; LOT – line of therapy; MI – myocardial infarction; NR – not reported; PI – proteasome inhibitor; PS – performance status; RI – renal insufficiency; SCT – stem-cell transplant; TFI – treatment-free interval; VRd – bortezomib, lenalidomide, dexamethasone.

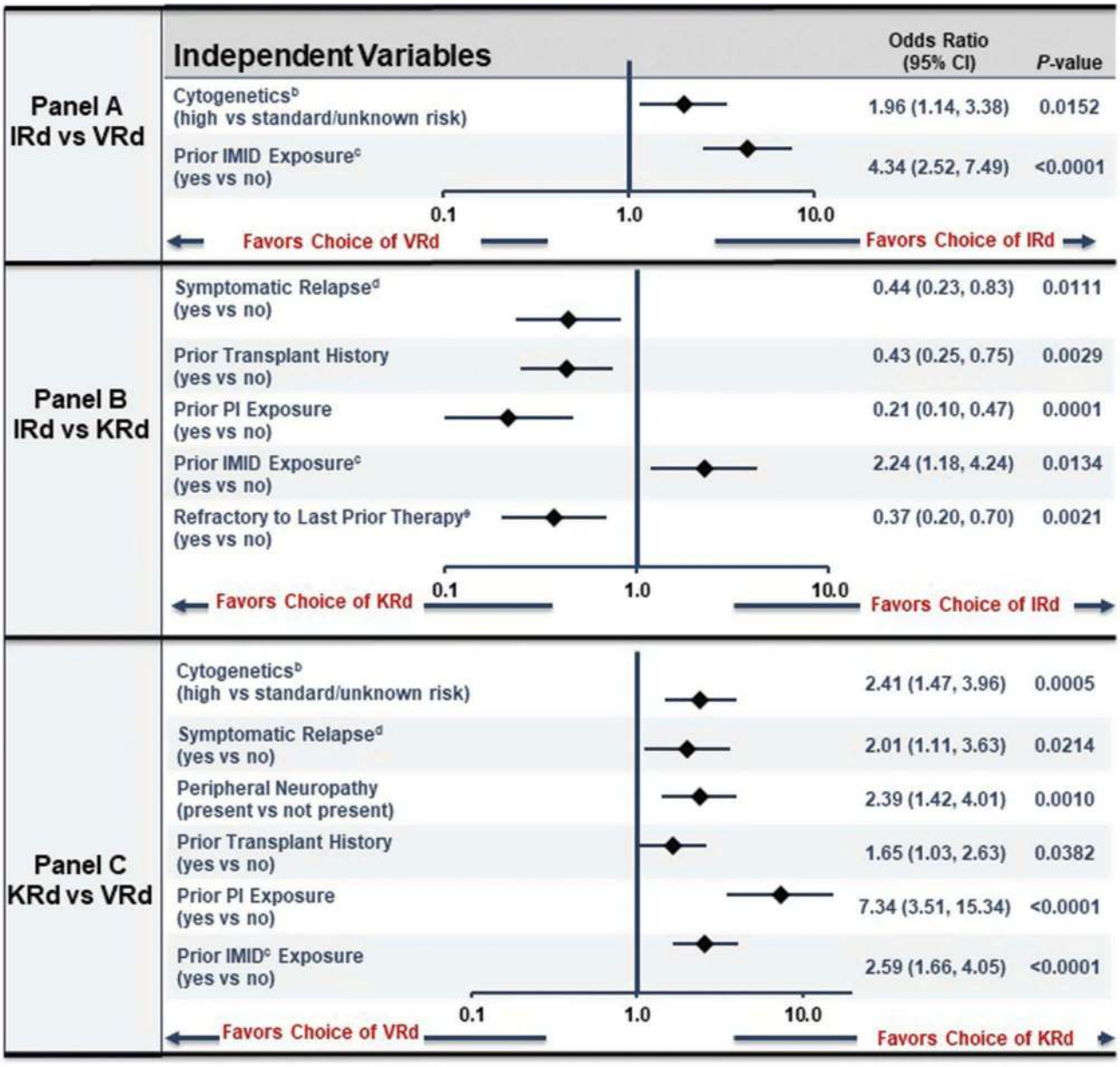


Figure 1. Significant factors independently associated with treatment choice[a]. [a]Covariates included modified frailty score (0 [fit], 1–2 [intermediate to frail]), baseline CRAB symptoms (hypercalcemia, renal failure, anemia, bone disease [yes vs. no]), cytogenetic risk (high, standard/unknown), ISS stage (I/II, III, unknown), prior IMID exposure, prior PI exposure, prior SCT, history of PN, CVD/uncontrolled HTN, time (months) from diagnosis to start of index LOT, refractory status to last therapy (yes, no [defined as a TFI from end of most previous LOT to initiation of index regimen of ≤60 days]), and time of first relapse (months [i.e. time from start of LOT1 to start of LOT2]). [b]Includes those for whom cytogenetics were unknown. [c]Greater than 96% of all prior IMID exposure was lenalidomide. [d]Defined as the presence of any CRAB symptoms (hypercalcemia, renal insufficiency, anemia, bone disease) at the start of the index regimen. [e]Defined as a TFI ≤60 days between most previous LOT and index LOT.

Key: CVD – cardiovascular disease; IMID – immunomodulatory drug; HTN – hypertension; IMID – immunomodulatory drug; IRd – ixazomib, lenalidomide, dexamethasone; ISS – International Staging System; KRd – carfilzomib, lenalidomide, dexamethasone; LOT – line of therapy; OR – odds ratio; PI – proteasome inhibitor; PN – peripheral neuropathy; SCT – stem-cell transplant; TFI – treatment-free interval; VRd – bortezomib, lenalidomide, dexamethasone.

0.75; $P = 0.0029$) or if they were refractory to the last line of therapy (OR: 0.37; 95% CI: 0.20, 0.70; $P = 0.0021$).

While we noticed a differential distribution of the modified frailty score (Table 1) by index regimen type, interestingly, frailty status utilizing the modified frailty score, which incorporated age and CCI only, was not independently associated with regimen choice (intermediate/frail$_{\text{modified frailty score}}$ vs. fit$_{\text{modified frailty score}}$ status, $OR_{IRd\ vs.\ VRd}$: 0.98; 95% CI: 0.59, 1.64; $P = 0.9386$), although lower odds of KRd receipt were observed among patients with intermediate/frail$_{\text{modified frailty score}}$ vs. fit$_{\text{modified frailty score}}$ status compared to VRd ($OR_{KRd\ v\ VRd}$: 0.69; 95% CI: 0.43, 1.12; $P = 0.1302$), but the results were not significant (Supplemental Table 5, Online Appendix). Also, after adjusting for other covariates, longer time from diagnosis for start of the index regimen did not emerge as an independent predictor of regimen choice in the LOT stratified analyses.

4.3. Duration of therapy

The median follow-up for all patients from initiation of the index LOT was 14.4 months (Interquartile range [IQR]: 6.7, 24.3); this varied by regimen (10.9 months, IRd; 14.8 months, KRd; 16.0 months, VRd). Overall, in LOT ≥2, median duration of therapy for the entire regimen within the index LOT was longest for those treated with IRd (12.3 months) vs. KRd (7.2 months) and VRd (10.0 months), with a significantly lower risk of IRd regimen discontinuation vs. KRd (HR: 0.71; 95% CI: 0.53, 0.95; $P = 0.0209$; Appendix Figure 3). The risks of discontinuation of the individual components (PI and lenalidomide) were both significantly lower in the IRd vs. KRd (HR_{PI}: 0.65, $P = 0.0034$; $HR_{lenalidomide}$: 0.64, $P = 0.0015$) or VRd (HR_{PI}: 0.62, $P = 0.0003$; $HR_{lenalidomide}$: 0.75, $P = 0.0312$) groups but comparable for the KRd vs. VRd (HR_{PI}: 0.94; $HR_{lenalidomide}$: 1.18; $P > 0.05$ for both) groups.

4.4. TTNT: stratified analysis

In stratified analysis by LOT (2–3 vs. ≥4), without adjustment for other covariates, the risk of initiation of next LOT or death was comparable for patients treated with IRd vs. VRd ($HR_{IRd\ vs.\ VRd}$: 1.01; 95% CI: 0.78, 1.30; $P = 0.9562$; median TTNT: 12.7 vs. 14.2 months) but was higher for those treated with KRd ($HR_{KRd\ vs.\ VRd}$: 1.33; 95% CI: 1.07, 1.66; $P = 0.0112$; median TTNT for KRd: 8.6 vs. 14.2 months). Further, patients initiating treatment with IRd in comparison to those with KRd had a lower risk of next LOT initiation or death ($HR_{IRd\ vs.\ KRd}$: 0.76; 95% CI: 0.58, 1.00; $P = 0.0470$) (Appendix Figure 4A).

These results were fairly consistent for patients treated in earlier LOTs (i.e. LOT 2 and 3; Appendix Figure 4B).

4.5. Multivariate analysis

Overall, after adjusting for baseline covariates to distinguish differences based on treatment effect, no differences in risk of initiation of next line therapy or death emerged ($P > 0.05$) for any of the comparisons across the PI-based Rd triplet regimens in the overall analysis of LOTs ≥2. The risk of initiation of the next LOT or death was comparable for patients treated in LOT ≥2 with IRd or KRd vs. VRd ($HR_{IRd\ vs.\ VRd}$: 0.93 [95% CI: 0.69, 1.26]; $HR_{KRd\ vs.\ VRd}$: 1.11 [95% CI: 0.84, 1.46]) and for IRd vs. KRd ($HR_{IRd\ vs.\ KRd}$: 0.84 [95% CI: 0.63, 1.13]). Adjusted median TTNTs for IRd, KRd, and VRd in LOT ≥2 were as follows: IRd: 13.5 months; KRd: 10.9 months; VRd 12.2 months (Figure 2, Panel A). Additionally, we undertook a sensitivity analysis restricting adjusted analyses of TTNT to only patients with known values for ECOG PS, ISS stage, and cytogenetic risk; the results from these analyses were consistent with the main analysis (Online Appendix, Table 6).

4.6. Multivariate subgroup analyses

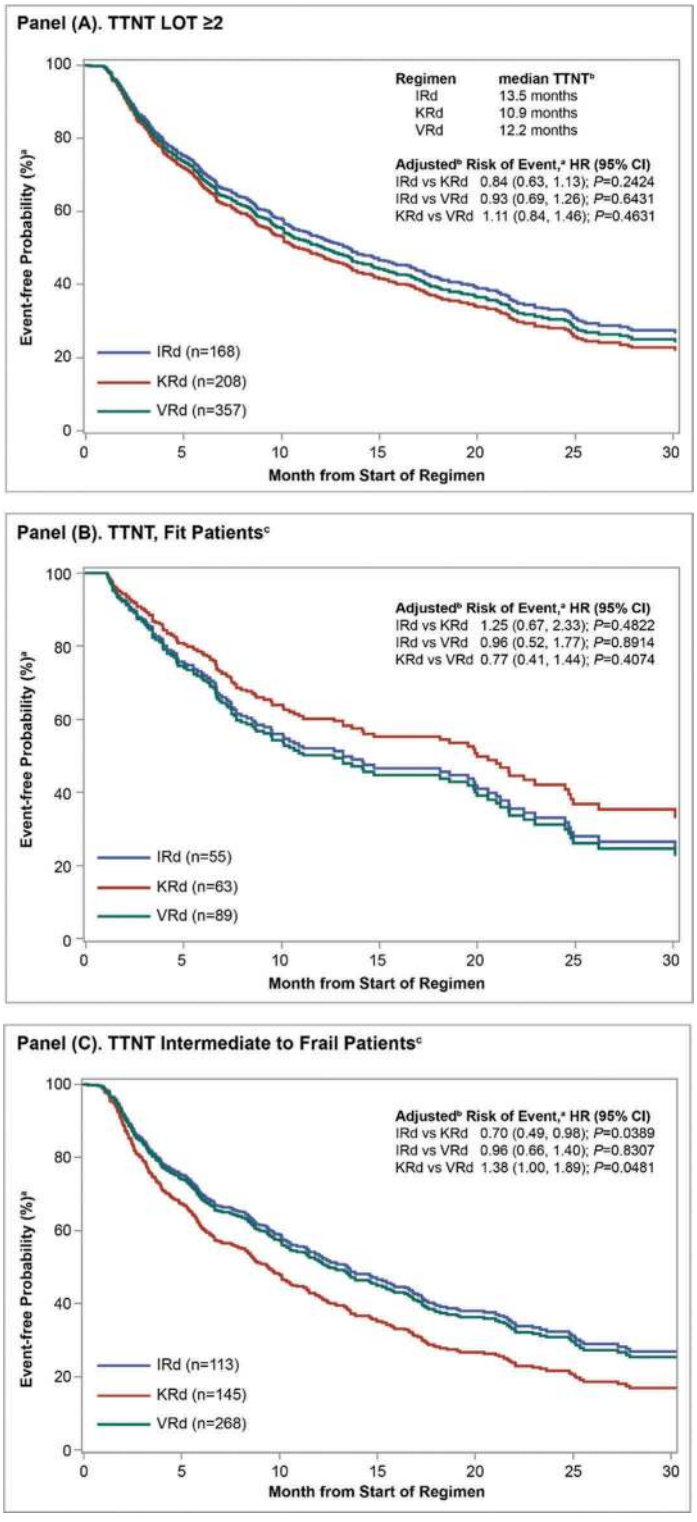
After adjustment for baseline covariates, differences in TTNT across the treatment groups were observed among patients deemed intermediate to frail via a modified frailty score, which considered age and CCI only (Figure 2, Panel C), but TTNT was comparable among fit patients (utilizing the modified frailty score), among patients treated in earlier LOTs (i.e. LOT 2 or 3), and for those with/without prior exposure to a PI (Appendix Figure 5). Specifically, prior exposure to bortezomib in LOT 1 did not lead to differences between the treatment groups for LOTS ≥2 (HR: 0.81, IRd vs. VRd; 1.07, KRd vs. VRd; 0.76, IRd vs. KRd; [$P > 0.05$ for all]), albeit numerically lower risks of next LOT initiation or death were noted for patients treated in LOT 2 with one of the other two PIs (K or I) after exposure to bortezomib in LOT 1 (HR: 0.44, IRd vs. VRd [$P = 0.0593$]; 0.69, KRd vs. VRd [$P = 0.3621$]; 0.64, IRd vs. KRd; [$P = 0.2452$]).

Among patients with a modified frailty score of intermediate to frail, the risk of initiation of next LOT or death was lower in the IRd vs. KRd group ($HR_{IRd\ vs.\ KRd}$: 0.70 [95% CI: 0.49, 0.98; $P = 0.0389$]), and it was higher in the KRd vs. VRd group ($HR_{KRd\ vs.\ VRd}$: 1.38 [95% CI: 1.00, 1.89; $P = 0.0481$]) (Figure 2(c) and Appendix Figure 5). The risk of next LOT initiation or death was comparable between those patients with a modified frailty score of intermediate to frail receiving IRd vs. VRd. Further, there were no differences in adjusted TTNT among any of the regimens for patients deemed as fit.

In a sensitivity analysis based on first use of the index regimen only (patient-level analysis), the TTNT results for LOT ≥2 and for all subgroups were consistent with the patient LOT-level analyses, which compared real-world use of the index regimens irrespective of sequencing order (Online Appendix, Table 1).

5. Discussion

In our population of real-world patients with RRMM engaged in routine care, some distinguishing differences in patient and disease characteristics based on the PI-Rd regimen choice were noted. For example, patients treated with KRd tended to be younger and were less likely to be frail by modified frailty score than those chosen for IRd or VRd. Further, patients who received VRd tended to be treated in LOT2 (VRd, 70%; KRd, 50%; IRd 37%), and fewer patients were refractory to previous PI and/or IMID therapy than those who received IRd or KRd. Conversely, patients initiating IRd were treated in later LOTs (3 or greater) and tended to have asymptomatic relapse with the absence of CRAB symptoms than those on KRd or VRd. In multivariate analyses after adjusting for prognostic and treatment selection-relevant factors, high-risk cytogenetic disease emerged as an independent predictor of treatment choice with IRd or KRd compared to VRd. Symptomatic relapse and relapse after a history of prior SCT were independently associated with KRd therapy compared to the other regimens, which reflects the proclivity among practitioners to utilize KRd in patients with a symptomatic relapse or more active disease, as evidenced by its increased use in our study in patients with relapse with end-organ damage (i.e. the presence of CRAB symptoms) or after previously intensive therapy (i.e. SCT). Prior to IMID and/or PI exposure was independently associated with lower odds of treatment with VRd vs. either of the other regimens, reflecting the use of VRd in earlier LOTs. Interestingly, frailty status (utilizing the modified frailty score) did not emerge as an independent predictor of treatment choice.



[a] Adjusted for the following covariates: index regimen type (IRd , KRd, VRd), modified frailty score (0 [fit], 1–2 [intermediate to frail]), prior PI and/or IMID exposure, prior SCT, history of CVD or uncontrolled HTN, history of PN, or baseline CRAB symptoms (hypercalcemia, renal failure, anemia, bone disease [all, yes vs. no]), cytogenetic risk (high, standard/unknown), ISS stage (I/II, III, unknown), PI/IMID refractory status (PI and/or IMID refractory, refractory to neither), time (months) from diagnosis to start of index LOT, refractory status to last therapy (yes, no; yes was defined as a TFI from end of most previous LOT to initiation of index regimen of ≤60 days), time of first relapse (months [i.e. time from start of LOT1 to start of LOT2), and year of diagnosis (2007–2011, 2012–2015, 2016–2018).

[b] An event was defined as the start of the next line of therapy or death

[c] Adapted from Palumbo, et al. (*Blood*. 2015;125(13):2068-2074) and includes age and CCI score only, as IADL and ADL were not available in the EHR database.

Key: CVD – cardiovascular disease; HTN – hypertension; IMID – immunomodulatory drug; IRd – ixazomib, lenalidomide, dexamethasone; ISS – International Staging System; KRd – carfilzomib, lenalidomide, dexamethasone; LOT – line of therapy; PI – proteasome inhibitor; PN – peripheral neuropathy; SCT – stem cell transplant; TFI – treatment-free interval; VRd – bortezomib, lenalidomide, dexamethasone.

Figure 2. Adjusted[a,b] Time to Next Therapy for All Patients (LOT ≥ 2) and by Modified Frailty Score[c]. (a) Adjusted for the following covariates: index regimen type (IRd, KRd, VRd), modified frailty score (0 [fit], 1–2 [intermediate to frail]), prior PI and/or IMID exposure, prior SCT, history of CVD or uncontrolled HTN, history of PN, or baseline CRAB symptoms (hypercalcemia, renal failure, anemia, bone disease [all, yes vs. no]), cytogenetic risk (high, standard/unknown), ISS stage (I/II, III, unknown), ECOG score (0-1, 2-4, unknown), PI/IMID refractory status (PI and/or IMID refractory, refractory to neither), time (months) from diagnosis to start of index LOT, refractory status to last therapy (yes, no; yes was defined as a TFI from end of most previous LOT to initiation of index regimen of ≤60 days), time of first relapse (months [i.e. time from start of LOT1 to start of LOT2]), and year of diagnosis (2007–2011, 2012–2015, 2016–2018). (b) An event was defined as the start of the next line of therapy or death. (c) Adapted from Palumbo et al. (*Blood*. 2015;125(13):2068–2074) and includes age and CCI score only, as IADL and ADL were not available in the EHR database.

Key: CVD – cardiovascular disease; HTN – hypertension; IMID – immunomodulatory drug; IRd – ixazomib, lenalidomide, dexamethasone; ISS – International Staging System; KRd – carfilzomib, lenalidomide, dexamethasone; LOT – line of therapy; PI – proteasome inhibitor; PN – peripheral neuropathy; SCT – stem-cell transplant; TFI – treatment-free interval; VRd – bortezomib, lenalidomide, dexamethasone.

Based on our real-world analysis, after adjusting for baseline covariates, no differences in TTNT emerged between any of the PI-Rd triplets overall. In adjusted subgroup analyses, our results revealed a TTNT benefit for IRd vs. KRd and worse TTNT for KRd vs. VRd among patients with intermediate/frail status as measured by the modified frailty score based on age and comorbidities, while a numerically longer TTNT was noted for KRd vs. both IRd and VRd among fit patients. Furthermore, patients who underwent a switch to either KRd or IRd after prior exposure to bortezomib in first line had numerically lower risks of next line of therapy initiation or death compared to VRd in second line.

The gap between the efficacy seen in trials and the actual effectiveness noted in this real-world analysis bears discussion. In contrast to the median TTNT of 14.2 months observed in this study for VRd, the phase 2 study of VRd yielded a median PFS of 9.5 months; however, 42% had disease that had progressed on or within 60 days of salvage therapy, and the median number of prior therapies was two in the trial [9]. This is indicative of treatment with VRd occurring in later LOTs within the phase 2 trial than in our real-world population chosen for VRd, in which 70% received only 1 prior LOT and most patients (86%) were not refractory to either an IMID or a PI at initiation of VRd. The efficacy/effectiveness gap was most striking for the KRd regimen. In contrast to the ASPIRE phase 3 clinical trial, which yielded a PFS in the KRd arm of 26.3 months, our population engaged in routine care who received KRd in LOT ≥2 and LOT 2–3 experienced a median TTNT of 8.6 and 9.5 months, respectively. This is despite the fact that more patients chosen for KRd in our study were treated in LOT 2 (50% vs. 39.8%) vs. in the ASPIRE trial; however, more patients initiating KRd in our study had known high-risk cytogenetics (28% vs. 13%, ASPIRE) and prior exposure to an IMID (with or without a PI) (73% vs. 59%, ASPIRE), and fewer patients in our study had relapsed after SCT prior to treatment with KRd (35% vs. 55%, ASPIRE) [10]. Our real-world findings mirror those of other observational studies of RRMM patients who received carfilzomib-containing regimens in lines 2–4 of therapy wherein the median TTNT/PFS ranged from 3.2 to 9.4 months [24–28]. Regarding therapy with the oral PI-Rd triplet combination, in the phase 3 TOURMALINE-MM1 study, IRd yielded a median PFS of 20.6 months, while our population had an unadjusted median TTNT of 12.7 months and 16.8 months among patients initiating therapy in LOT ≥2 and LOT 2–3, respectively [16]. Again, differences in patient selection that may contribute to this discrepancy include LOT in the phase 3 trial of IRd, LOT 2 for 60% of patients vs. 37% in this study, and the number of patients with previous IMID exposure (54%, TOURMALINE-MM1 vs. 86%, here) [16]. The real-world results for IRd are more varied. Our findings reveal that our real-world population treated with ixazomib (with 63% treated in ≥3 LOT) had a shorter TTNT (12.7 months for all patients treated in LOT ≥2) than the PFS reported in other registry-based analyses. The median PFS in the registry studies ranged from 20.9 to 23.1 months in populations where IRd was used as second-line therapy for ≥50% of patients; however, notably in these analyses, in addition to earlier use of IRd, the patient population was younger (median age 66–67 years) and approximately 61% of patients in those studies had undergone an SCT and had a longer time from diagnosis to IRd initiation of 42 months [29,30,]. In our study, the TTNT for patients treated with IRd in earlier LOTs (n = 116; 53% in LOT2 and 47% in LOT3) of almost 17 months (Appendix Figure 4) more closely approximates the reported PFS in the aforementioned registry analyses.

These discrepancies between efficacy and effectiveness highlight the known limited generalizability of clinical trial findings where elderly and comorbid patients are underrepresented among those treated in routine clinical care. Notably, patients with a modified frailty score of intermediate to frail, representing 71.8% of the cohort in our study (intermediate, 47.2%; frail, 24.6%), had a lower adjusted risk of next treatment initiation or death with IRd compared to KRd and a higher risk of next treatment initiation or death with KRd compared to VRd. Yet, frailty status utilizing the modified frailty score did not emerge as an independent determinant of regimen choice. These results suggest that a more individualized patient selection may attenuate the efficacy-effectiveness gap.

In addition to patient factors differentiating real-world vs. clinical trial populations, duration of therapy also frequently differs. In this analysis, we observed a lower risk of discontinuation of the PI and IMID component in the IRd vs. the KRd and the VRd group. Several studies have shown that treatment to progression or longer duration of therapy is associated with longer survival outcomes [17,31–34]. The independent association between duration of therapy and outcomes by PI-Rd regimen type was outside the scope of this analysis and warrants further study.

This study must be interpreted in the context of limitations inherent to all nonrandomized observational studies, which include the possibility of residual confounding due to unobserved treatment selection biases. Refractory status to either a PI or an IMID was defined using a previously published algorithm [23] and may over- or underestimate the true proportion of refractory patients. As previously mentioned, a modified frailty score utilizing only age and CCI was employed in this study based on the work of Palumbo et al. [14], but this modified measure, which does not include physician-reported measures of activities of daily living (ADL, IADL), may underestimate the proportion of patients with intermediate and frail status. Comorbidities also tend to be underreported in EHR datasets. The lack of an association between CVD/uncontrolled HTN and regimen choice in this analysis needs to be interpreted with caution and requires further research. While in our study, we utilized an approach for capture of cardiovascular diseases based on ICD-9/-10 that is accepted as standard in other retrospective database studies [35,36,], in order to identify clinically relevant cardiovascular comorbidities in our elderly population and identify only symptomatic cases, we restricted capture of these codes to a primary or discharge diagnosis [12], which may have contributed to under-estimation of CVD in our elderly RRMM population.

Real-world data collected in the course of routine care have commonly been associated with the limitation of missing or unavailable data. For example, response rates or depth of response to therapy were not available for any patient. Further, we found that 67.8% had a missing ECOG performance status, 72.4% of patients had a missing ISS stage and

79.5% did not have cytogenetic results available. With respect to the identification of cytogenetic risk, as our natural language processing algorithm was developed to specifically query the presence of high-risk cytogenetic anomalies, those with missing values (categorized as unknown) may be, in large part, comprised of patients without high-risk features (i.e., standard-risk patients). Other real-world data sources have similarly reported high proportions of missing data for prognostic markers. For example, the Connect MM prospective registry of 1,493 newly diagnosed MM patients treated at 259 US sites, including community (81%) and academic centers (18%) in the US, reported that only 58.7% and 58.1% of patients had a record of ISS stage or a FISH/cytogenetic analysis, respectively, with 8.3% of patients having unspecified/failed cytogenetic test results among those tested [37]. Another large retrospective US real-world data source had missing ISS stage for 76% of MM patients (data on file). In part, these rates of missing data may reflect the limited adoption of these prognostic markers in treatment selection in routine care, lack of access to timely testing, testing failure, or underreporting in secondary data sources [37]. In our multivariate analyses, we mitigated possible bias stemming from missing values for these prognostic factors by incorporating other covariates that are related to the kinetics of disease aggressiveness, including time from initiation of frontline therapy to first relapse, time from diagnosis to initiation of the index LOT, and LOT number. In addition, we undertook a sensitivity analysis restricting adjusted analysis of TTNT to only patients with known ECOG PS, ISS stage, and cytogenetic risk; the results from these sensitivity analyses were consistent with the main analysis (Online Appendix, Table 6). Further, the analyses, including subgroup analyses, were not powered for statistical comparisons; therefore, results may differ with more recent data with longer follow-up and/or a larger sample size. Specific to cytogenetics, it was not feasible to conduct a subgroup analysis by PI-triplet received for patients with high cytogenetic risk, due to high level of censoring in this subgroup. This does, however, highlight a need for future analyses to address differences in outcomes by treatment received for prognostically important subgroups, namely those with high cytogenetic risk.

6. Conclusions

In this real-world representative RRMM cohort, after controlling for baseline characteristics, the PI-Rd triplet combinations were comparable in TTNT among all patients treated in LOT ≥2. However, TTNT was shorter with KRd vs. the other PI-Rd combinations in patients who had a modified frailty score of intermediate/frail, while a numerically longer adjusted TTNT was noted for KRd among fit patients. Furthermore, patients who underwent a switch to either KRd or IRd after prior exposure to bortezomib in first line had numerically lower risks of next line of therapy initiation or death compared to VRd in second line. We also observed a longer duration of therapy with the PI and IMID component in the IRd vs. the KRd and the VRd group. The relative impact of longer duration of the oral PI-Rd vs. other triplets on outcomes warrants further research. The TTNT results from our RRMM cohort suggest a gap between the efficacy observed in clinical trials and a lower effectiveness in the real world, which was especially striking for KRd, underlining the limited generalizability of results from randomized clinical trials, where 50–75% of patients are excluded due to inability to meet eligibility criteria [12]. Individualized treatment recommendations based on patient characteristics, such as advanced age and/or comorbidity status (which comprised our modified frailty score), may help improve real-world outcomes; this is especially pertinent in an elderly RRMM population as demonstrated by the real-world effectiveness results in this study.

Author Contributions

Contribution: AC, DR, and SA conceived the study and AC, DR, AR, LC, MB, EF, AP, and SA aided in study design. AC, PGR, DR, MAD, PS, ET, RH, MB, EF, AR, LC, HH, and SA collected, assembled, analyzed, and interpreted data; DR and MB wrote the manuscript; and all authors approved the final manuscript.

Funding

This paper was funded by Takeda Pharmaceuticals Company Limited.

Declaration of interest

A Chari receives Consulting honoraria and/or research support received from Pharmacyclics, Takeda, Celgene, Novartis, Amgen, Janssen, Bristol-Myers Squibb, Array Biopharma, The Binding Site, Seattle Genetics, and Adaptive Biotechnology; S Ailawadhi receives Consulting honoraria and/or research support received from Takeda, Pharmacyclics, Amgen, Janssen, and Celgene; P Richardson receives Consulting honoraria and/or research support received from Jazz Pharmaceuticals, Celgene, and Oncopeptides; D Romanus is an Employee of Takeda; M Dimopoulos receives Consulting honoraria and/or research support received from: Genesis Pharma, Amgen Inc, Celgene Corporation, Janssen Biotech Inc, Onyx Pharmaceuticals, an Amgen subsidiary, and Takeda Oncology, Amgen Inc; P Sonneveld receives consulting honoraria and/or research support received from Amgen, Celgene/BMS, Janssen, Karyopharm, Oncopeptides, and Takeda; E Terpos receives Consulting honoraria and/or research support received from Amgen, Celgene, Genesis, Janssen, Takeda, Bristol-Myers Squibb BMS, and Medison; R Hajek receives Consulting honoraria and/or research support received from Takeda, Novartis, Celgene, PharmaMar, Oncopeptides, Janssen, Amgen, AbbVie, and Bristol-Myers Squibb; A Raju, M Blazer, and E Farrelly are all employees of Xcenda; A Palumbo, L Cain, and H Huang are all employees of Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

ORCID

Ajai Chari http://orcid.org/0000-0002-0405-7480
Meletios A. Dimopoulos http://orcid.org/0000-0001-8990-3254
Pieter Sonneveld http://orcid.org/0000-0002-0808-2237
Evangelos Terpos http://orcid.org/0000-0001-5133-1422

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. SEER: Surveillance, epidemiology, and end results program; cancer stat facts: myeloma. [cited 2019 Sep 17]. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html
2. Howell D, Smith A, Appleton S, et al. Multiple myeloma: routes to diagnosis, clinical characteristics and survival – findings from a UK population-based study. Br J Haematol. 2017;177:67–71.

3. Pozzi S, Marcheselli L, Bari A, et al. Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis. Br J Haematol. 2013;163:40–46.
4. Rondeau V, Cornet E, Moreau P, et al. Prediction of patients with multiple myeloma eligible for second- or third-line treatment in France. Ann Hematol. 2016;95:1307–1313.
5. Al-Hamadani M, Hashmi SK, Go RS. Use of autologous hematopoietic cell transplantation as initial therapy in multiple myeloma and the impact of socio-geo-demographic factors in the era of novel agents. Am J Hematol. 2014;89:825–830.
6. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111:2516–2520.
7. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28:1122–1128.
8. Durie B, Hoering A, Abidi M, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017a;389:519–527.
9. Richardson PG, Xie P, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. Blood. 2014;123(10):1461–1469.
10. Stewart AK, Rajkumar SV, Dimopoulus MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372:142–152.
•• **This is a hallmark trial of a novel triplet (PI-Rd) combination in patients with RRMM that had received 1-3 prior therapies.**
11. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374:1621–1634.
•• **This is a hallmark trial of a novel triplet (PI-Rd) combination in patients with RRMM that had received 1-3 prior therapies.**
12. Chari A, Romanus D, Palumbo A, et al. Randomized clinical trial representativeness and outcomes in real-world patients: comparison of 6 hallmark randomized clinical trials of relapsed/refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2020 Jan;20(1):8–17.e16.
•• **This is a real-world study showing the ineligibility for clinical trials of >50% of RRMM patients engaged in routine care.**
13. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer J. 2018 Nov 9;8(11):109.
14. Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015;125(13):2068–2074.
•• **This publication evaluates frailty as a negative prognostic factor for survival among patients with MM.**
15. Cook G, Jackson GH, Morgan GJ, et al. The outcome of high-dose chemotherapy and auto-SCT in patients with multiple myeloma: a UK/Ireland and European benchmarking comparative analysis. Bone Marrow Transpl. 2011;46:1210–1218.
16. Chan EHL, De-Silva D, Lin AHF, et al. Clinical benefit of depth of response for relapsed/refractory multiple myeloma patients treated on clinical trials: retrospective analysis from two tertiary centres. Br J Haematol. 2019;186(1):162–165.
17. Palumbo A, Bringhen S, Larocca A, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. J Clin Oncol. 2014;32(7):634–640.
•• **This study provides evidence that treatment to progression or prolonged duration of therapy impacts overall survival.**
18. Van Beurden-Tan CHY, Blommestein HM, Zweegman S, et al. The relationship of response on time to next treatment based on evidence from two RCTs in newly diagnosed stem cell transplantation ineligible multiple myeloma patients. Blood. 2016;128(22):2141.
19. Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived from ICD-9-CCM administrative data. Med Care. 2002 Aug;40(8):675–685.
20. Nash Smyth E, Conti I, Wooldridge JE, et al. Frequency of skeletal-related events and associated healthcare resource use and costs in US patients with multiple myeloma. J Med Econ. 2016;19(5):477–486.
21. NCCN.org [Internet]. National comprehensive cancer network clinical practice guidelines in oncology (NCCN Guidelines®) for Multiple Myeloma V.1.2020. [cited 2019 Sept 18]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.
• **These are consensus guidelines on how to treat both NDMMand RRMM patients which are updated at least annually orwith the availability of new data/evidence**
22. Rajkumar SV, Harousseau JL, Durie B, et al. International myeloma workshop consensus panel 1. Consensus recommendations for the uniform reporting of clinical trials: report of the International myeloma workshop consensus panel 1. Blood. 2011;117(18):4691–4695.
23. Usmani S, Ahmadi T, Ng Y, et al. Analysis of real-world data on overall survival in MM patients with ≥3 prior lines of therapy including a PI and an IMID, or double refractory to a PI and an IMID. Oncologist. 2016;21:1–7.
24. Danhof S, Schreder M, Rasche L, et al. Efficacy and safety of pre-approval carfilzomib-based therapy of multiple myeloma in daily practice - experience from a German academic center. Clin Lymphoma Myeloma Leuk. 2015;15(3):e284.
25. Durie B, Cook G, Goldschmidt H, et al. The use of carfilzomib and bortezomib in routine clinical practice: results from preamble, an ongoing, observational cohort study in multiple myeloma. Haematologica. 2017b;102(s2):520. Abstract E1269.
26. Cerchione C, Ferrara K, Peluso I, et al. Carfilzomib-lenalidomide-dexamethasone in the management of relapsed and refractory multiple myeloma: a real-life experience. Haematologica. 2017;102(S2):804.
27. Hobbs M, Paludo J, Fonder A, et al. Efficacy of carfilzomib (K), pomalidomide (P), and dexamethasone (d) in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM) in a real world setting. Blood. 2016;128:3337.
28. Romanus D, Raju A, Yong C, et al. Association between treatment regimen type in second-line therapy (2LT) and duration of therapy (DOT) & time to next treatment (TTNT) in a United States (US) relapsed/refractory multiple myeloma (RRMM) Cohort. Clin Lymphoma Myeloma Leuk. 2017;17(1 supplement):e81–e82.
29. Hajek R, Terpos E, Lee HC, et al. Lenalidomide-dexamethasone (IRd) in relapsed/refractory multiple myeloma (MM) patients (Pts) - effectiveness in routine clinical practice is similar to the efficacy in the phase 3 TOURMALINE-MM1 trial: a pooled analysis from the Insight MM observational study and the czech registry of monoclonal gammopathies (RMG). Blood. 2018;132(Suppl 1):1971.
30. Minarik J, Krhovska P, Jelinek T, et al. Treatment of relapsed and refractory multiple myeloma with fully oral triplet IRD (ixazomib, lenalidomide and dexamethasone) is safe and with significant therapeutic outcomes. Blood. 2018;132(Suppl 1):1959.
31. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018 Jan 18;131(3):301–310.
•• **This study provides evidence that treatment to progression or prolonged duration of therapy impacts overall survival.**
32. Bringhen S, Mateos MV, Zweegman S, et al. Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica. 2013;98:980–987.
•• **This publication evaluates negative prognostic factors for survival among patients with MM.**
33. Mateos MV, Richardson PG, Dimopoulos MA, et al. Effect of cumulative bortezomib dose on survival in multiple myeloma patients receiving bortezomib-melphalan-prednisone in the phase III VISTA study. Am J Hematol. 2015;90(4):314–319.
•• **This study provides evidence that treatment to progression or prolonged duration of therapy impacts overall survival.**
34. Hari P, Romanus D, Palumbo A, et al. Prolonged duration of therapy is associated with improved survival in patients treated for

relapsed/refractory multiple myeloma in routine clinical care in the United States. Clin Lymphoma Myeloma Leuk. 2018;18:152–160.

•• **This real-world analysis provides evidence that prolonged duration of therapy impacts overall survival.**

35. Hershman DL, Accordino MK, Shen S, et al. Association between nonadherence to cardiovascular risk factor medications after breast cancer diagnosis and incidence of cardiac events. Cancer. 2020:1–9. doi: 10.1002/cncr.32690

36. Heslinga M, Nielen MMJ, Smulders Y, et al. Amplified prevalence and incidence of cardiovascular disease in patients with inflammatory arthritis and coexistent autoimmune disorders. Rheumatology. 2020:1–7. pii: kez650. doi: 10.1093/rheumatology/kez650.

37. Rifkin RM, Abonour R, Terebelo H, et al. Connect MM Registry: the importance of establishing baseline disease characteristics. Clin Lymphoma Myeloma Leuk. 2015;15(6):368–376.