haematologica
Journal of the Ferrata Storti Foundation

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Received: May 1, 2024.
Accepted: August 16, 2024.

Citation: Alissa Visram, Kelvin Kar-Wing Chan, Hsien Seow, Gregory Pond, Anastasia Gayowsky, Ghulam Rehman Mohyuddin, Arleigh McCurdy, Irwindeep Sandhu, Christopher Venner, Guido Lancman, Amaris Balitsky, Tom Kouroukis, Robert Bruins, Shaji Kumar, Rafael Fonseca, and Hira Mian. Comparing the clinical trial efficacy versus real-world effectiveness of treatments for multiple myeloma: a population-based study.
Haematologica. 2024 Aug 22. doi: 10.3324/haematol.2024.285768 [Epub ahead of print]

Comparing the clinical trial efficacy *versus* real-world effectiveness of treatments for multiple myeloma: a population-based study

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Running title: Clinical trial versus real-world outcomes in myeloma

Funding: Myeloma Canada

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Author Disclosures:
No relevant COI

Acknowledgements:
This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This study also received funding from Myeloma Canada. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. Parts of this material are based on data and/or information compiled and provided by CIHI, the Ontario Ministry of Health, and Ontario Health (OH). The analyses, conclusions, opinions and statements expressed herein

are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Data sharing:
The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Phase 3 randomized control trials (RCTs) are the “gold standard” used to obtain marketing and regulatory approval for novel MM treatments, inform patients about treatment outcomes, and inform treatment guidelines. Yet, numerous indirect real-world (RW) and RCT comparisons have shown that RW patient tend to have inferior outcomes compared to RCT patients. However, to date, no study has directly *quantified* the differences in outcomes between RW and RCT patients with MM treated with standard of care (SoC) therapies. Understanding and quantifying the difference in *efficacy*, the outcome in an “ideal” RCT setting, and *effectiveness*, the outcome in the “real life” clinical practice setting, is needed to contextualize the generalizability of RCT data to the general population. To fill this knowledge gap, we conducted a population-based cohort study to compare and quantify the difference in the RW effectiveness versus RCT efficacy of SoC MM regimens with respect to the progression free survival (PFS) and overall survival (OS).

The RCT cohort was identified from registrational phase III RCTs which led to the public reimbursement of SoC regimens in Ontario between January 1, 2013 to December 31, 2021. Regimens included lenalidomide/dex [**Rd**] bortezomib/Rd [**VRd**] in patients with transplant ineligible newly diagnosed multiple myeloma patients [**TIE-NDMM**]. Relapsed refractory MM (**RRMM**) regimens included carfilzomib/Rd [**KRd**], carfilzomib/dex [**Kd**], daratumumab/Rd [**DRd**], daratumumab/bortezomib/dex [**DVd**], and pomalidomide/dex [**Pd**]. The most recent published Kaplan-Meier PFS (1-7) and OS (1, 2, 7-11) curves were manually digitized using the WebPlotDigitizer software (version 4.6), then reconstructed using an established algorithm (12) to provide individual patient-level estimates of PFS and OS for the experimental arm in the RCT cohorts.

Real-world data was obtained using from Ontario’s ICES administrative database. Ontario has a universal, publicly funded healthcare system which provides access to chemotherapy, and the provincial administrative database captures virtually all health care encounters and has a loss to follow up rate of 0.25%. Treatment data was accessed through the Ontario Drug Benefit database for regimens containing only oral medications and the Cancer Activity Level Reporting database for treatment regimens containing injected or infused medications. Patients diagnosed with MM between January 1, 2013 to December 31, 2020 and initiating treatment with SoC regimens either at diagnosis or relapse were included in this study. Provincial reimbursement criteria for SoC regimens mirrors the RCT inclusion criteria, with regards to the prior drug exposure and lines of therapy (see **table s1**). The data cut-off date was May 31, 2022.

We assessed the efficacy and effectiveness of RCT and RW data, respectively, by comparing the Kaplan-Meier survival curve estimates of PFS and OS. The RCT PFS was defined as the time from index regimen treatment to disease progression, death, or last follow-up, whichever occurred first. In RW administrative database, the progression date could not be accurately determined and so time to next treatment (TTNT) was used as a surrogate for RW PFS. TTNT was defined as the time from initiation of index regimen to initiation of subsequent MM treatment, death, or last follow-up. In both RCT PFS and RW TTNT definitions, patients remaining on the index regimen at last follow up were censored. OS was defined as the time from initiation of the index treatment to death or end of follow-up. Meta-analyses using random effects models were used to compare the PFS and OS outcomes of RW versus RCT patients. Effect estimates for PFS and OS were summarized using hazard ratios (HR). The study was approved by the ethics committee of McMaster University.

Overall, 3951 RW and 2476 RCT MM patients, treated with 7 SoC MM regimens, were included. Baseline characteristics of the RW and RCT cohorts are shown in **table 1**. Overall, the RW cohort patients tended to be older than RCT patients. A minority of TIE-NDMM patients treated were initially started on short course of single agent lenalidomide or bortezomib during the COVID-19 pandemic and then transitioned

to the full triplet regimen. For RRMM SoC regimens, the time between MM diagnosis and index regimen treatment initiation was longer in the RCT versus RW cohorts. However, despite RW patients being treated with the SoC regimens earlier in their disease course, apart from RW patients treated with Pd, RW patients tended to have higher rates of previous lenalidomide and bortezomib exposure.

The RW had 51% increased risk of progression or death compared to RCT patients (pooled HR 1.51 [95% CI 1.03-2.21], p=0.034, **figure 1a**). Six of the seven SoC regimens analyzed had a shorter mPFS in the RW cohort compared to the RCT cohort (**table 2, figure s1**). The disparate PFS outcomes were more apparent in patients treated with RRMM regimens (pooled HR 1.66 [95% CI 0.99-2.80], p=0.056, absolute decrease in mPFS ranged from 7.2-18.3 months in the RW cohort) as opposed to NDMM regimens (pooled HR 1.16 [95% CI 1.03-1.31], p=0.012, absolute decrease in mPFS ranged from 3-8.2 months in the RW cohort). Even after excluding previously lenalidomide/bortezomib exposed patients in the TIE-NDMM VRd RW cohort, the RW cohort had a trend towards poorer PFS and poorer OS outcomes compared to the RCT cohort (PFS HR 1.12 [95% CI 0.81-1.55]; OS HR 2.037 [95% CI 1.38-3.02]). Similarly, RW patients had a worse OS compared to RCT patients treated with 6 of the 7 regimens, with a 76% higher risk of death (pooled HR 1.76 [95% CI 1.31-2.36], p<0.001, **figure 1b**) and an absolute median OS ranging from 19.3-37.9 months lower than RCT patients.

We then stratified outcomes age and baseline comorbidity index (see **table s2**). Older adults tended to have slightly longer mPFS but similar mOS (which may reflect slower transitions to next line therapy at time of relapse), while patients with more baseline comorbidities had shorter mPFS and mOS estimates. Overall, the mPFS and mOS were consistently lower in the RW versus RCT cohorts.

This is the first study directly quantifying the significant difference in RCT efficacy and RW effectiveness of SoC MM treatments. Our study's strengths include our data source - a large database comprehensively capturing treatment in a universal healthcare system with minimal loss to follow up, with patients treated in both academic and community centers - thereby providing an accurate RW assessment of health outcomes.

The main contributors to the efficacy-effectiveness gap are likely differences in patient selection and the regimen administration or adherence between RW and RCT cohorts. It is well known that the stringent RCT inclusion criteria and mandatory drug washout periods often excludes patients with highly aggressive or proliferative disease. RW patients in this study had a shorter time from diagnosis to initiation of the index regimen and higher rates of prior drug exposure, suggesting they may have been more heavily pretreated compared to RCT patients which may explain why the efficacy-effectiveness gap was most apparent for RRMM regimens. RW patients in our study also tended to be older than RCT patients, and had a high comorbidity burden, and would likely not have met the stringent RCT inclusion criteria. Prior studies have similarly shown that up to 70% of RW patients would have been excluded from landmark RCT's based on their baseline age, comorbidities, cytopenias, or organ function (13-15). Lastly, RCTs have strict protocols that require close patient monitoring and pre-specified dose reductions based on reported adverse events. However, RW patients may have lower adherence or may have received lower doses of the SoC regimens which could have compromised outcomes.

Given limitations in our data availability within our administrative database, we could not assess how patient-level disease data (i.e. cytogenetic risk, baseline staging, prior treatment exposure and refractoriness) may have contributed to the efficacy-effectiveness gap. Another significant limitation was our use of TTNT as a surrogate for PFS in the RW cohort, as is often done in real world observational studies. However, previous studies have shown that TTNT and PFS are comparable endpoints, and that TTNT may overestimate RW PFS due to delays in starting next-line therapy until significant biochemical

or clinical progression. This is likely especially true in our study given the limited number of reimbursed treatment lines in our public-payer healthcare system. However, if treatment was switched due to intolerance or prior to meeting progression criteria, then TTNT may underestimate PFS. Lastly, our study reflects outcomes within the Canadian healthcare system where access to therapies is limited by public reimbursement. While our drug access is comparable to many other public healthcare systems in the developed world, our RW outcomes may not be as generalizable to patient populations with increased treatment accessibility.

In conclusion, this is one the largest population-level studies highlighting the significant efficacy-effectiveness gap between registrational RCTs and RW usage of these regimens, with RW patients experiencing a 51% higher risk of progression or death, and a 76% higher risk of death compared to RCT patients. Future studies focusing on closing the efficacy-effectiveness gap may involve designing trials that better represent real-world scenarios using pragmatic trial designs, or more inclusive eligibility criteria. Our data emphasize the importance of ongoing evaluation of RW data to further contextualize effectiveness of therapy and facilitate shared treatment decisions among patients and clinicians.

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Table 1. Comparison of baseline characteristics and outcomes of patients treated with multiple myeloma regimens as part of standard of care in the real world versus and in the corresponding randomized clinical trial

	TIE-NDMM				RRMM									
	VRd		Rd		Kd		KRd		DVd		DRd		Pd	
	RW (n=282)	SWOG S0777 (n=242)	RW (n=824)	FIRST (n=535)[a]	RW (n=498)	ENDEAVOUR (n=464)	RW (n=287)	ASPIRE (n=396)	RW (n=627)	CASTOR (n=251)	RW (n=785)	POLLUX (n=286)	RW (n=648)	MM-003 (n=302)
Median age at treatment initiation - years (IQR or range)	75 (IQR 73-79)	63 (IQR 56-70)	79 (IQR 74-84)	73 (range 44-91)	68 (IQR 61-74)	65 (IQR 58-72)	68 (IQR 59-73)	64 (range 38-87)	70 (IQR 63-76)	64 (range 30-88)	72 (IQR 65-77)	65 (range 34-89)	70 (IQR 62-77)	64 (range 34-84)
Male sex - n (%)	160 (57)	153 (63)	452 (55)	294 (55)	287 (58)	240 (52)	177 (62)	215 (54)	355 (57)	NR	454 (58)	NR	365 (56)	181 (60)
CCI[b] - n (%)														
≥2	116 (41)	NR	335 (41)	NR	425 (85)	NR	246 (86)	NR	507 (81)	NR	564 (72)	NR	521 (80)	NR
<2	166 (59)	NR	489 (59)	NR	73 (15)	NR	41 (14)	NR	120 (19)	NR	221 (28)	NR	127 (20)	NR
Median months between diagnosis and treatment initiation - n (IQR or range)	1 (IQR 1-5)	NR	2 (IQR 1-12)	NR	45 (IQR 27-70)	NR	25 (IQR 15-48)	36 (range 5-236)	43 (IQR 27-68)	46 (range 8-248)	35 (IQR 20-59)	42 (range 5-324)	47 (IQR 28-72)	64 (range 7-360)
Prior exposure at treatment initiation - n (%)														
Lenalidomide	102 (36)	0	0	0	464 (93)	177 (38)	187 (65)	79 (20)	597 (95)	89 (36)	515 (66)	50 (18)	585 (90)	302 (100)
Thalidomide	0	0	0	0	*1-5	211 (45)	*1-5	NR[b]	0	125 (50)	*1-5	122 (43)	*1-5	173 (57)
Pomalidomide	0	0	0	0	158 (32)	NR	*21-25	NR[b]	49 (8)	NR	*1-5	2 (<1)	33 (5)	0
Ixazomib	*1-5	0	0	0	58 (12)	NR	*15-19	NR	60 (10)	NR	76 (10)	2 (<1)	70 (11)	NR
Bortezomib	33 (12)	0	0	0	468 (94)	250 (54)	264 (92)	261 (66)	504 (80)	162 (65)	749 (95)	241 (84)	582 (90)	302 (100)
Carfilzomib	0	0	0	0	31 (6)	2 (<1)	8 (3)	NR	48 (8)	NR	62 (8)	6 (2)	124 (19)	NR
Isatuximab	0	0	0	0	*6-10	NR	0	NR	0	NR	0	0	*1-5	NR
Daratumumab	0	0	0	0	188 (38)	NR	6 (2)	NR	20 (3)	NR	15 (2)	0	115 (18)	NR
Transplant	0	0	0	0	320 (64)	NR	142 (49)	217 (55)	387 (62)	157 (63)	345 (44)	180 (63)	333 (51)	214 (71)

[a]Continuous Rd arm
[b]ASPIRE trial reported that 39% (n=154) of the KRd group had prior exposure to pomalidomide or thalidomide
[c]Calculated using the Deyo-modified CCI
Abbreviations: charlson comorbidity index (**CCI**); multiple myeloma (**MM**); newly diagnosed transplant ineligible MM (**TIE-NDMM**); relapsed refractory MM (**RRMM**); real world (**RW**); randomized control trial (**RCT**); not reported (**NR**); interquartile range (**IQR**); lenalidomide & dex (**Rd**); bortezomib & Rd (**VRd**); carfilzomib & dex (**Kd**); carfilzomib & Rd (**KRd**); daratumumab & bortezomib & dex (**DVd**); daratumumab & Rd (**DRd**); Pomalidomide & dex (**Pd**); median progression free survival (**mPFS**); median overall survival (**mOS**)
*Given confidentiality regulations with IC/ES data, subgroups representing <5% of the population cannot be enumerated, and therefore an estimate range of the number of patients is provided.

Table 2. Summary of mPFS and mOS in the RW and RCT cohorts

	mPFS (95% CI) - months		mOS (95% CI) - months	
	RW	**RCT**	**RW**	**RCT**
Rd	**23** (21.1-26.9)	**26** (20.2-29.6)[a]	**38.4** (34.3-40.3)	**59.1** (54.7-66.3)[a]
VRd	**32.6** (25.1-44.2)	**40.8** (33.1-51.1)	**48.1** (43.5-66.1)	**NR** (79.9-NR)[b]
Kd	**3.9** (3.1-4.8)	**18.7** (15.6-NR)	**9.9** (8.4-12.3)	**47.8** (41.9-NR)[a]
KRd	**8** (6.2-9.6)	**26.3** (23.3-30.5)	**21.6** (17.8-28.7)	**48.3** (42.4-52.8)
DVd	**9.5** (8.4-10.8)	**16.7** (13.3-19.6)[a]	**25.9** (22.1-30.9)	**49.6** (42.2-62.3)
DRd	**32.6** (27.8-NR)	**44.5** (34.1-NR)	**48.3** (41.9-NR)	**67.6** (53.1-80.5)
Pd	**5** (4.4-6)	**4** (3.6-4.7)	**12.6** (10.7-14.5)	**12.7** (10.4-15.5)

[a]95% CI are generated from RCT individual patient data from the digitized published Kaplan-Meier curves, as these values were not present in the publication text
[b]At a median follow up of 84 months (2), the mOS of VRd was not reached (and therefore the mOS is at least 84 months)
Abbreviations: median progression free survival (**mPFS**); median overall survival (**mOS**); real world (**RW**); randomized clinical trial (**RCT**); confidence interval (**CI**); lenalidomide & dex (**Rd**); bortezomib & Rd (**VRd**); carfilzomib & dex (**Kd**); carfilzomib & Rd (**KRd**); daratumumab & bortezomib & dex (**DVd**); daratumumab & Rd (**DRd**); Pomalidomide & dex (**Pd**); transplant ineligible newly diagnosed multiple myeloma (**TIE-NDMM**); relapsed refractory multiple myeloma (**RRMM**); proteosome inhibitor (**PI**)

Figure 1. Meta-analysis of the progression free survival (PFS) and overall survival (OS) in the RW and RCT cohorts. Panel A) summarizes the progression free survival (PFS) and panel B) overall survival (OS) in RW versus RCT patient cohorts with MM, stratified by regimens used in the newly-diagnosed MM (NDMM) versus relapsed refractory MM (RRMM) treatment setting. Abbreviations: lenalidomide & dex (Rd); bortezomib & Rd (VRd); carfilzomib & dex (Kd); carfilzomib & Rd (KRd); daratumumab & bortezomib & dex (DVd); daratumumab & Rd (DRd); Pomalidomide & dex (Pd)

A) **Regimen** **Hazard Ratio (95% CI)**

NDMM Regimens

Rd	1.15 (1.01-1.31)
VRd	1.24 (0.95-1.62)
Subtotal	**1.16 (1.03-1.31)**

Heterogeneity: $Tau^2 = 0.000$; $Chi^2 = 0.244$, df = 1 (P = 0.621); $I^2 = 0.00\%$
Test for overall effect: Z = 2.507 (P = 0.012)

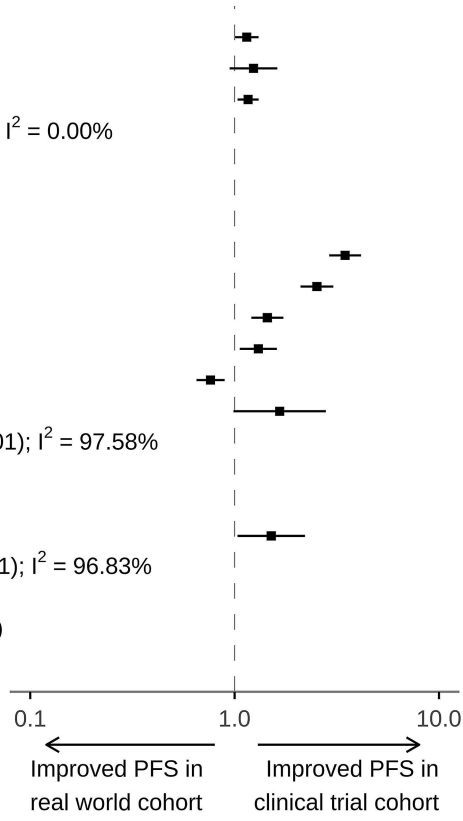
RRMM Regimens

Kd	3.47 (2.90-4.15)
KRd	2.53 (2.10-3.04)
DVd	1.45 (1.21-1.73)
DRd	1.31 (1.06-1.61)
Pd	0.76 (0.65-0.89)
Subtotal	**1.66 (0.99-2.80)**

Heterogeneity: $Tau^2 = 0.344$; $Chi^2 = 183.936$, df = 4 (P < 0.001); $I^2 = 97.58\%$
Test for overall effect: Z = 1.910 (P = 0.056)

Total **1.51 (1.03-2.21)**

Heterogeneity: $Tau^2 = 0.254$; $Chi^2 = 203.551$, df = 6 (P < 0.001); $I^2 = 96.83\%$
Test for overall effect: Z = 2.126 (P = 0.034)
Test for subgroup differences: $Chi^2 = 1.700$, df = 1 (P = 0.192)



B) **Regimen** **Hazard Ratio (95% CI)**

NDMM Regimens

Rd	1.64 (1.42-1.89)
VRd	2.38 (1.72-3.30)
Subtotal	**1.92 (1.33-2.75)**

Heterogeneity: $Tau^2 = 0.053$; $Chi^2 = 4.207$, df = 1 (P = 0.040); $I^2 = 76.23\%$
Test for overall effect: Z = 3.522 (P < 0.001)

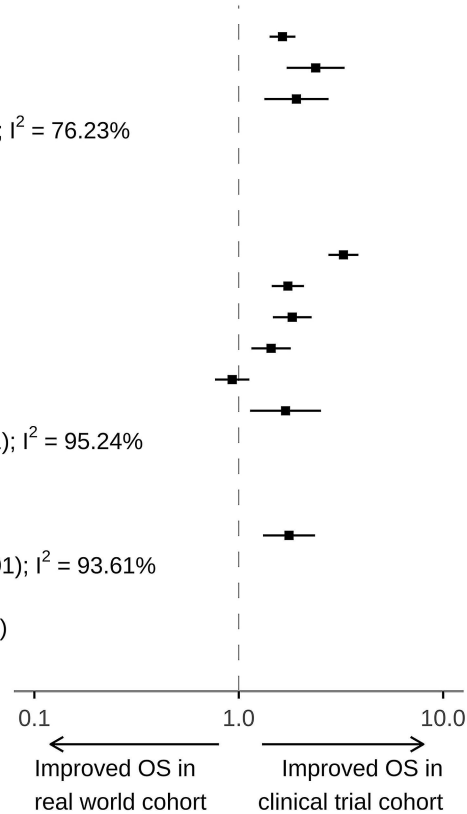
RRMM Regimens

Kd	3.25 (2.75-3.85)
KRd	1.74 (1.45-2.09)
DVd	1.83 (1.47-2.27)
DRd	1.44 (1.15-1.80)
Pd	0.93 (0.77-1.13)
Subtotal	**1.69 (1.14-2.53)**

Heterogeneity: $Tau^2 = 0.198$; $Chi^2 = 95.794$, df = 4 (P < 0.001); $I^2 = 95.24\%$
Test for overall effect: Z = 2.584 (P = 0.010)

Total **1.76 (1.31-2.36)**

Heterogeneity: $Tau^2 = 0.145$; $Chi^2 = 100.043$, df = 6 (P < 0.001); $I^2 = 93.61\%$
Test for overall effect: Z = 3.786 (P < 0.001)
Test for subgroup differences: $Chi^2 = 0.200$, df = 1 (P = 0.655)



Supplementary Appendix

Table S1. Comparison of clinical trial inclusion criteria and Cancer Care Ontario (CCO) drug regimen funding. The CCO criteria that differ from RCT trial inclusion/exclusion criteria are bolded.

	CCO criteria				RCT inclusion criteria			
Regimen	Funding date	Patient population	Prior lines	Prior drug exposure/ refractory requirements	Date of first publication	Prior lines	Inclusion criteria (based on prior treatment)	Exclusion criteria (based on prior treatment)
Pd	February 6, 2015	RRMM	-	Bortezomib and lenalidomide refractory. **No requirement for prior alkylator exposure**	September 3, 2013 (12)	-	bortezomib refractory or intolerance AND lenalidomide refractory AND alkylator exposure	Prior pomalidomide exposure
Rd	March 14, 2017	TIE-NDMM	None	Same as trial	September 4, 2014 (5)	None	No prior treatment	-
KRd	May 1, 2018	RRMM	**≥1**	Same as trial	January 8, 2015 (8)	1-3	Prior bortezomib and lenalidomide exposure allowed	Lenalidomide refractory
Kd	May 1, 2018	RRMM	1-3	If prior PI exposure, **no requirement to be PI unexposed within 6 months pre-treatment. Otherwise, same as trial**.	December 5, 2015 (9)	1-3	Prior bortezomib and carfilzomib exposure allowed (6-month PI treatment free interval before enrollment required)	Bortezomib or carfilzomib refractory
DVd	March 15, 2019	RRMM	≥1	Same as trial	August 25, 2016 (11)	≥1	-	Bortezomib refractory (or intolerant) OR Proteosome inhibitor refractory
DRd	March 15, 2019	RRMM	≥1	Same as trial	October 6, 2016 (10)	≥1	-	Lenalidomide refractory (or intolerant)
VRd	December 16, 2020	TIE-NDMM	None	Same as trial	February 4, 2017 (6)	None	No prior treatment	-

Abbreviations: lenalidomide & dex (Rd); bortezomib & Rd (VRd); carfilzomib & dex (Kd); carfilzomib & Rd (KRd); daratumumab & bortezomib & dex (DVd); daratumumab & Rd (DRd); Pomalidomide & dex (Pd); transplant ineligible newly diagnosed multiple myeloma (TIE-NDMM); relapsed refractory multiple myeloma (RRMM); proteosome inhibitor (PI)

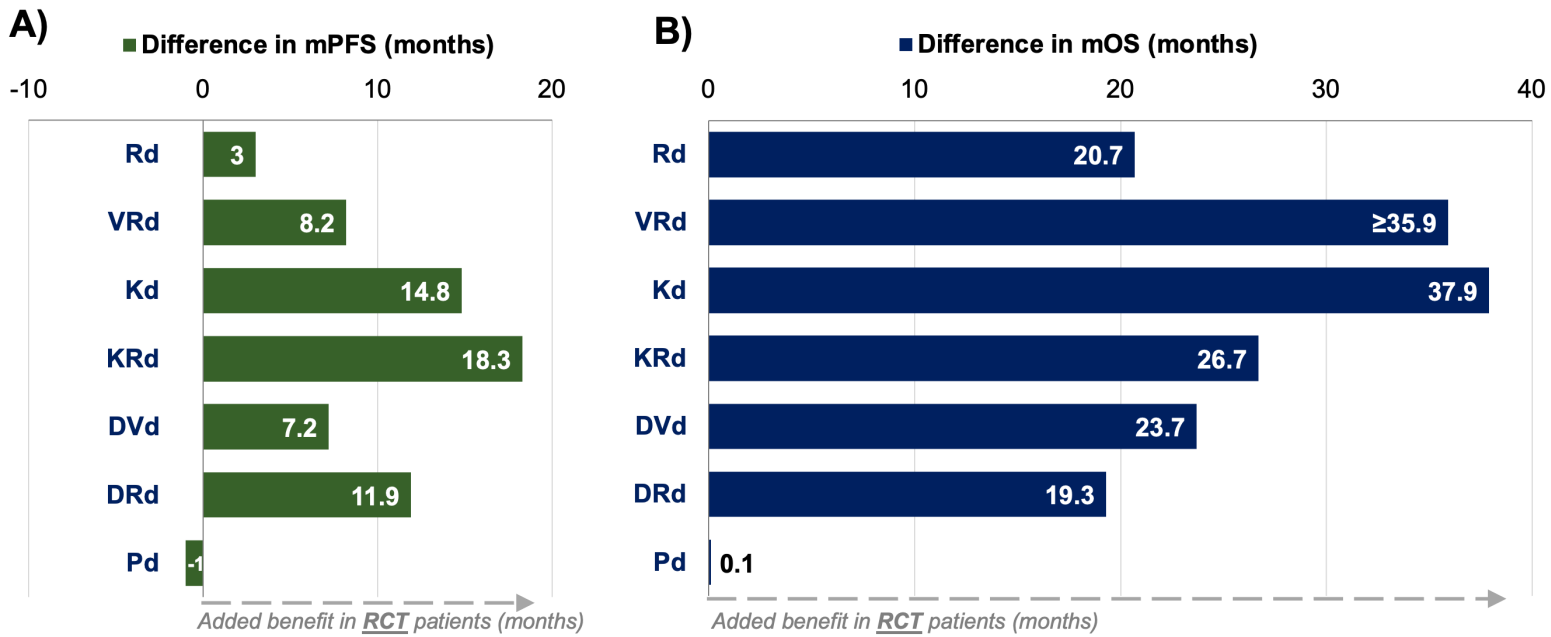


Figure S1. Difference in absolute the median A) PFS and B) OS between clinical trial (RCT) and real-world (RW) patient cohorts. A positive number represents an improved PFS or OS, respectively, in the CT cohort compared to the RW cohort. In the SWOG0777 VRd study, the median OS was not reached in the VRD CT cohort at 84 months of follow up, and therefore the absolute improvement in OS noted is at least 35.9 months compared to the RW cohort. Abbreviations: lenalidomide & dex (Rd); bortezomib & Rd (VRd); carfilzomib & dex (Kd); carfilzomib & Rd (KRd); daratumumab & bortezomib & dex (DVd); daratumumab & Rd (DRd); Pomalidomide & dex (Pd)

Table S2. Summary of mPFS and mOS in the RW cohort, stratified by baseline age

	Number of patients		mPFS		mOS	
	Age <70	**Age ≥70**	**Age <70**	**Age ≥70**	**Age <70**	**Age ≥70**
RD	49	775	25.5 (20-39.5)	22.9 (20.7-26.9)	37.5 (29.7-64.2)	38.4 (34.3-40.4)
VRD	26	256	14.1 (5.2-NR)	32.6 (25.1-44.2)	28.4 (5.5-NR)	52.7 (43.5-NR)
KD	287	211	3.8 (2.8-4.6)	4.3 (2.9-5.7)	9.9 (8.4-13.5)	9.9 (7.3-13)
KRD	169	118	6.3 (4.7-8.6)	9.6 (7.3-11.7)	21.6 (17.2-30.1)	21.9 (13.9-32.3)
DVD	304	323	8.7 (7-9.9)	10.9 (8.7-14.5)	29.8 (22.4-40.3)	23.2 (18.5-30.2)
DRD	310	475	27.8 (21.2-NR)	NR (28.6-NR)	NR (45.2-NR)	43.4 (38.6-NR)
PD	318	330	3.9 (3.3-5.1)	6.1 (5-7.6)	13.6 (11.6-17.3)	10.5 (9.3-14)
	CCI <2	**CCI ≥2**	**CCI <2**	**CCI ≥2**	**CCI <2**	**CCI ≥2**
RD	489	335	26 (22.5-31.3)	20 (16.1-23.5)	45.3 (38.7-49.5)	29 (23.5-35)
VRD	166	116	35.8 (25.6-44.2)	24.3 (16.1-NR)	48.1 (43.5-NR)	52.7 (26.8-NR)
KD	73	425	7.6 (5.4-10.2)	3.3 (2.8-4.1)	20.5 (12.3-38.6)	8.6 (7.1-10.5)
KRD	41	246	9.7 (5.7-14)	8 (5.6-9.4)	35 (20.2-59.5)	21.2 (16.7-27.9)
DVD	120	507	12.6 (8.5-17.8)	9 (7.7-10.5)	33.2 (22.8-NR)	24.2 (20-30.2)
DRD	221	564	NR (34.8-NR)	27.5 (22.6-34)	NR (NR-NR)	43.4 (35.8-NR)
PD	127	521	6.4 (5-8.3)	4.6 (3.9-5.6)	16.6 (12.3-21.8)	11.6 (9.9-13.5)

Abbreviations: charlson comorbidity index (**CCI**); median progression free survival (**mPFS**); median overall survival (**mOS**); real world (**RW**); randomized clinical trial (**RCT**); confidence interval (**CI**); lenalidomide & dex (**Rd**); bortezomib & Rd (**VRd**); carfilzomib & dex (**Kd**); carfilzomib & Rd (**KRd**); daratumumab & bortezomib & dex (**DVd**); daratumumab & Rd (**DRd**); Pomalidomide & dex (**Pd**); transplant ineligible newly diagnosed multiple myeloma (**TIE-NDMM**); relapsed refractory multiple myeloma (**RRMM**); proteosome inhibitor (**PI**)