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RESEARCH ARTICLE

Long-term follow-up of outcomes including progression-free survival 2 in patients with transplant-ineligible multiple myeloma in the real-world practice: A multi-institutional report from the Canadian Myeloma Research Group (CMRG) database

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Abstract

Multiple myeloma remains an incurable cancer mostly affecting older adults and is characterized by a series of remission inductions and relapses. This study aims to evaluate the outcomes in newly diagnosed transplant-ineligible patients using bortezomib/lenalidomide-based regimens in the Canadian real world as well as their

outcomes in the second line. The Canadian Myeloma Research Group Database (CMRG-DB) is a national database with input from multiple Canadian Centres with now up to 8000 patients entered. A total of 1980 transplant ineligible patients were identified in the CMRG-DB between the years of 2007–2021. The four most commonly used induction regimens are bortezomib/melphalan/prednisone (VMP) (23%), cyclophosphamide/bortezomib/dexamethasone (CyBorD) (47%), lenalidomide/dexamethasone (Rd) (24%), and bortezomib/lenalidomide/dexamethasone (VRd) (6%). After a median follow-up of 30.46 months (0.89–168.42), the median progression-free survival (mPFS) and median overall survival (mOS) of each cohort are 23.5, 22.9, 34.0 months, and not reached (NR) and 64.1, 51.1, 61.5 months, and NR respectively. At the time of data cut-off, 1128 patients had gone on to second-line therapy. The mPFS2 based on first-line therapy, VMP, CyBorD, Rd, and VRd is 53.3, 48.4, 62.7 months, and NR respectively. The most common second-line regimens are Rd (47.4%), DRd (12.9%), CyBorD (10.3%), and RVd (8.9%) with a mPFS and a mOS of 17.0, 31.1, 15.4, and 14.0 months and 34.7, NR, 47.6, 33.4 months, respectively. This study represents the real-world outcomes in newly diagnosed transplant-ineligible myeloma patients in Canada. The spectra of therapy presented here reflect the regimens still widely used around the world. While this is sure to change with anti-CD38 monoclonal antibodies now reflecting a new standard of care in frontline therapy, this cohort is reflective of the type of multiple myeloma patient currently experiencing relapse in the real-world setting.

KEYWORDS
MM, transplant-ineligible

1 | INTRODUCTION

Despite improved therapeutics leading to unprecedented response rates in multiple myeloma (MM), the condition remains incurable and patients frequently cycle through multiple lines of therapy. We have previously published data from the Canadian Myeloma Research Group Database (CMRG-DB), on the outcomes of newly diagnosed transplant-ineligible MM (ND-TIMM) patients treated with either bortezomib-based treatments or lenalidomide and dexamethasone [1]. These were the standard of care regimens for many years based on published, phase 3 data from the VISTA [2] and FIRST [3] trials, respectively. The substitution of melphalan for cyclophosphamide has since become the preferred alkylator backbone in combination with bortezomib based on a phase 2 study [4]. The original CMRG paper sought to observe outcomes between these two regimens in the real-world setting given the lack of randomized data. The median progression-free survival (PFS) was significantly longer for lenalidomide and dexamethasone compared to bortezomib-based therapy as was the median treatment duration, while overall survival (OS) was similar.

Now, we present updated data with longer follow-up of regimens used in treating ND-TIMM patients, including PFS2 data, after the front-line use of bortezomib/lenalidomide/dexamethasone (VRd) [5], bortezomib/melphalan/prednisone (VMP), cyclophosphamide/bortezomib/dexamethasone (CyBorD), and lenalidomide/dexamethasone (Rd). More contemporary trials have used these treatments as control arms and results indicate similar outcomes to initial reports for these regimens. For example, the control arm in the phase 3 ALCYONE trial was VMP which gave a PFS of approximately 19 months [6]. Rd was used as a control arm in multiple phase 3 studies with reported PFS outcomes ranging between 22 and 34 months [7–9]. We also report the subsequent therapies received among TIMM patients in the real world, when the approved first-line regimens were VMP, CyBorD, Rd, and VRd in Canada.

2 | MATERIALS AND METHODS

2.1 | Patient population

The CMRG-DB, a national database with input from multiple Canadian centers, now contains over 8000 patients. Patients with a diagnosis of MM as per the International Myeloma Working Group (IMWG) were included if they were previously untreated and were transplant ineligible. Transplant eligibility was defined in accordance with individual institutional guidelines and physician selection. Patients not receiving therapy, those with other plasma cell dyscrasias, and those

in whom autologous stem cell transplant was planned as part of first-line therapy were excluded. Fluorescence in situ hybridization (FISH) was performed at diagnosis and documented in all available cases. Patients harboring a t(4;14), t(14;16), or del(17p) were classified as having high-risk disease; all other cases were considered as standard risk unless the test was not performed in which case they were coded as "unknown". Entry of source data into the CMRG-DB is approved by local research ethics boards at every contributing site. The approval for review of this specific dataset was obtained from the Jewish General Hospital institutional review board as per the approved governance structure of the CMRG-DB and in accordance with the Declaration of Helsinki.

2.2 | Bortezomib containing regimens, Rd, and VRd regimens

The bortezomib-containing regimens (BCR) included CyBorD/P and VMP. The selection of a particular bortezomib regimen and subsequent dose reductions were made at the discretion of the individual treating physician, and as such, there is a certain heterogeneity in the way it was given across the country. Rd was given to patients according to standard guidelines and dose modifications were allowed at the physician's discretion. VRd was also given with once-weekly subcutaneous bortezomib, with lenalidomide and dexamethasone dosing adjusted as per the treating physician [10].

2.3 | Study outcomes

The efficacy outcomes included overall response rate (ORR), PFS, and OS. Disease response was assessed based on modified IMWG guidelines. In patients whose complete response could not be confirmed due to the absence of a bone marrow biopsy, the response was classified as a very good partial response (VGPR). PFS was defined as the time of treatment initiation to progression, death, or last follow-up. The PFS after second-line therapy was defined as the time from second-line therapy to progression, death, or last follow-up. PFS2 was defined as the time from initiation of first-line therapy to progression, death, or last follow-up after second-line therapy. OS was measured from the time of treatment initiation to death or last follow-up.

2.4 | Statistical analysis

Descriptive statistics were used to report standard baseline characteristics of all MM transplant-ineligible patients in the database. Categorical variables including sex, myeloma isotype, ISS stage, cytogenetic risk, the spectrum of therapies used, and best response were summarized with counts and percentages. Continuous variables including lactate dehydrogenase (LDH), creatinine, duration of treatment, time to progression, and time to death were summarized with means, standard deviation, medians, and/or ranges as appropriate.

Statistical hypothesis testing was used to determine differences in baseline and outcome variables. Chi-squared or Fisher's exact tests (as appropriate) were used to determine differences in baseline and outcome variables among categorical variables. Wilcoxon-Mann-Whitney and Kruskal-Wallis tests (as appropriate) were used to determine differences in baseline and outcome variables among continuous variables.

Time-to-event analyses were used to assess PFS and OS. Survival curves were constructed according to the Kaplan-Meier method and the impact of covariates of interest was assessed using the log-rank test. The Cox proportional hazards regression model was used to determine the joint effect of covariates for PFS and OS.

Multivariable analysis was used to assess the impact of various risk factors on OS, PFS, and PFS2. A stepwise forward selection process was used to select the covariates included in forest plot multivariable analyses; only covariates with a p-value < 0.10 were included. Hazard ratios were reported with 95% confidence intervals.

Statistical analyses were performed using R core team 2020 (R-4.1.1), Vienna, Austria, and RStudio team 2019 (RStudio-1.4.1717) for Windows. All p-values were 2-sided and for the statistical analyses, $p < 0.05$ was considered to indicate a statistically significant result.

3 | RESULTS

A total of 1980 ND-TIMM patients were included. Of these, 156 (8%) were treated on a clinical trial in the first line and also included in this analysis. Baseline characteristics are shown in Table 1. The average age for the whole group was 73. High-risk cytogenetics accounted for 28% of evaluable cases. Fifty-two percent of patients had unknown or missing FISH results. Most patients were treated with CyBorD (47%), then Rd (24%), VMP (23%), and VRd (6%). Clinical characteristics were not statistically significantly different between treatment groups, except for a higher creatinine level in the CyBorD/P group ($p < 0.001$). Also, the number of patients with high-risk cytogenetics was greater in the VRd and CyBorD/P groups compared to Rd ($p < 0.0001$). The most common cause of treatment discontinuation of first-line therapy was progressive disease, which occurred in 45% of patients after a median follow-up of 30.5 months (0.89–168.42). The subsequent main cause of treatment discontinuation was toxicity with 16% of patients stopping due to this reason. In order to focus on the more contemporary therapy, 115 patients received VRd in the first line and the majority of these patients were still in remission on this treatment at the time of data cut-off. Nine patients died during first-line therapy and 21 patients relapsed on this therapy. Subsequent treatments included CyBorD, daratumumab-bortezomib-dexamethasone. Eight patients received other therapies that were not clearly defined.

At the time of data cut-off, 1128 patients had received second-line therapy. The majority of those who received a BCR in the first line received a lenalidomide-based regimen in the second line, and vice versa (Figure 1). The most common second-line regimens were

TABLE 1 Demographic and clinical characteristics for transplant-ineligible myeloma patients receiving front-line treatment ($n = 1980$).

Characteristic	CyBorD/P ($n = 932$)	VMP/D ($n = 460$)	L/Ld/p ($n = 473$)	VRd ($n = 115$)	Total ($n = 1980$)
Male gender, *n* (%)	557 (59.8)	261 (56.7)	267 (56.4)	69 (60.0)	1154 (58.3)
Age at Tx initiation, median (range)	70 (35–99)	75 (32–92)	77 (51–98)	76 (45–89)	73 (32–99)
Myeloma isotype					
IgG, *n* (%)	504 (57.9)	278 (66.0)	275 (61.5)	67 (59.8)	1124 (60.8)
IgA, *n* (%)	181 (20.8)	95 (22.6)	104 (23.3)	34 (30.4)	414 (22.4)
Light chain only, *n* (%)	167 (19.2)	44 (10.5)	62 (13.9)	8 (7.1)	281 (15.2)
Others, *n* (%)	18 (2.1)	4 (1.0)	6 (1.3)	3 (2.7)	15 (1.7)
Unknown or missing	62	39	26	3	130
ISS Staging					
Stage I	132 (17.6)	55 (16.3)	85 (23.6)	27 (28.7)	299 (19.4)
Stage II	229 (30.5)	141 (41.8)	140 (38.8)	27 (28.7)	537 (34.8)
Stage III	390 (52.0)	141 (41.8)	136 (37.7)	40 (42.6)	707 (45.8)
Unknown or Missing	181	123	112	21	437
Beta 2 microglobulin, median (range)	458 (24.6–8142.5)	399 (57.6–7192.5)	372 (110.0–3163.7)	356 (34.5–8130)	416 (24.6–8142.5)
Albumin, g/L, median (range)	35 (14–51)	34 (12–51)	36 (10–56)	39 (24–48)	35 (10–56)
Calcium, mmol/L, median (range)	2.4 (1.2–23.0)	2.3 (1.6–4.0)	2.4 (1.2–9.0)	2.6 (2.1–20.9)	2.4 (1.2–23.0)
Creatinine > 177 umol/L, *n* (%)	244(27.8)	84(20.1)	25(5.5)	17(15.3)	370(19.9)
Unknown or Missing	54	42	18	5	119
Elevated LDH, > 250 U/L, *n* (%)	173 (24.5)	55 (19.2)	69 (16.8)	11 (10.5)	308 (20.4)
Unknown or Missing	226	174	62	11	473
FISH cytogenetics					
t(4;14), *n* (%)	67 (11.1)	14 (7.0)	18 (7.4)	12 (13.2)	111 (9.7)
Unknown or Missing	327	259	228	24	838
17p, *n* (%)	90 (14.5)	23 (11.2)	25 (10.2)	14 (15.7)	152 (13.1)
Unknown or Missing	311	255	228	26	820
t(14;16), *n* (%)	28 (5.4)	3 (2.5)	6 (3.1)	5 (7.3)	42 (4.7)
Unknown or Missing	415	342	282	46	1085
Cytogenetic risk classification					
High Risk, *n* (%)	159 (29.3)	37 (26.8)	45 (23.2)	24 (33.8)	265 (28.0)
Standard Risk, *n* (%)	383 (70.7)	101 (73.2)	149 (76.8)	47 (66.2)	680 (72.0)
Unknown or missing	390	322	279	44	1035
Regimen as received part of clinical trials *n* (%)	7 (0.8)	9 (2.0)	126 (26.6)	14 (12.2)	156 (7.9)

CyBorD/P, cyclophosphamide, bortezomib, dexamethasone/prednisone; ISS, international staging system; LDH, lactate dehydrogenase; L/Ld/p, lenalidomide dexamethasone/prednisone; VMP/D, bortezomib, melphalan, prednisone/dexamethasone; VRd, bortezomib, lenalidomide, dexamethasone.

Rd (47.4%), DRd (12.9%), CyBorD (10.3%), and VRd (8.9%). Among the 852 patients (43%) who did not receive second-line therapy, 402 (20%) of patients are still alive, 314 (16%) have died and 136 (7%) are lost to follow-up. Of the patients still alive, 223 (11%) completed first-line therapy as planned and are on observation and 179 (9%) are still on first-line treatment and responding. Twenty-two patients (1%) that completed first-line therapy, progressed without the initiation of a subsequent line of therapy.

3.1 | Efficacy endpoints

The ORR (and ≥ VGPR) was 75.4% (45.9%) in the VMP group, 79.7% (53.6%) in the CyBorD/P group, 67.4% (42.9%) in the Rd group, and 75.4% (60.9%) in the VRd group. VRd induced a statistically higher ≥ VGPR rate compared to Rd and VMP ($p < 0.0005$ and 0.004 respectively), but no statistical significance when compared to CyBorD. The median duration of treatment for each of these groups is 9.23

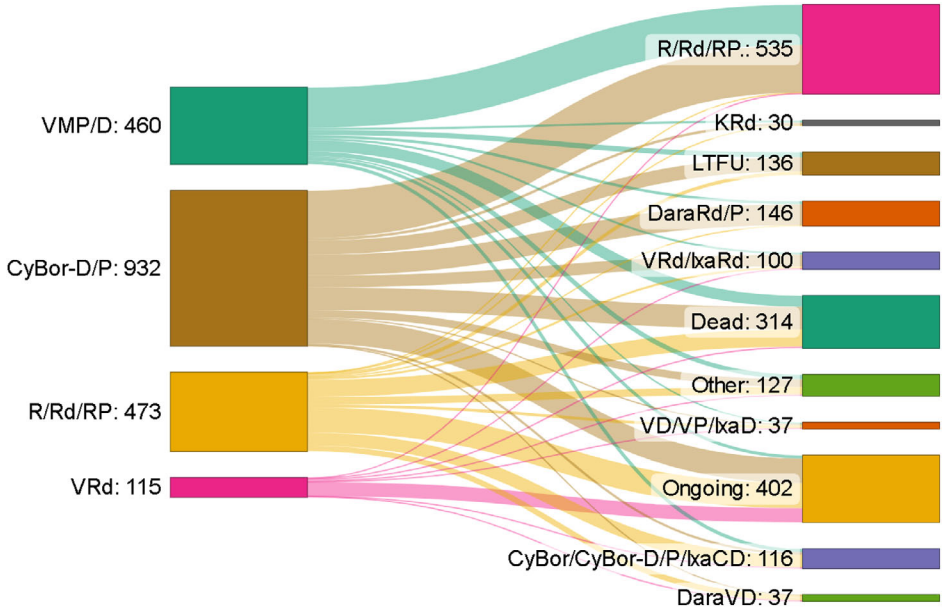

FIGURE 1 Sankey diagram of the anti-myeloma therapies subsequent to front-line therapy based on choice of first-line.

TABLE 2 Primary clinical efficacy endpoints by type of front-line therapy.

Treatment regimen	ORR ≥ PR	Response ≥ VGPR	Duration of treatment median per month (range)	PFS (Median months and 95% CI)	OS (Median months and 95% CI)
VMP/D, *n* (%)	347 (75.4)	211 (45.9)	9.23 (0–53.9)	24.0 (21.9–27)	64.8 (59.5–71.5)
CyBorD, *n* (%)	742 (79.7)	500 (53.6)	7.4 (0–78.4)	23.4 (21.1–26)	51.1 (47.1–57.6)
Ld, *n* (%)	319 (67.4)	203 (42.9)	12.3 (0–129)	34.2 (21.9–27)	65.2 (54–74.7)
VRd, *n* (%)	87 (75.4)	70 (60.9)	7.3 (0.20–44.6)	NR (28.5–NR)	NR (44.6–NR)

CyBorD, cyclophosphamide, bortezomib, dexamethasone; Ld, lenalidomide, dexamethasone; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression free survival; VGPR, very good partial response; VMP/D, bortezomib, melphalan, prednisone/dexamethasone; VRd, bortezomib, lenalidomide, dexamethasone.

(0.86–53.9), 7.4 (0.46–78.4), 12.3 (0.22–129), and 7.3 (0.13–44.60) months, respectively (taking into account the BCR are generally finite in nature). (Table 2)

After a median follow-up of 30.5 months (0.89–168.42), the median PFS and OS were 26.2 (24.5–27.8), and 58.4 months (54.2–62.8) respectively for the entire group. By treatment subgroups, the median PFS of the VMP, CyBorD/P, Rd, and VRd groups were 24 months (21.9–27), 23.4 months (21.1–26), 34.2 months (29.2–42.8), and not reached (NR) (28.5–NR), respectively. VRd demonstrated a statistically significant improved PFS over the other regimens (Table 2). There was no difference between the CyBorD and VMP groups. The median PFS2 was 60.0 (50.1–67.3) months after VMP, 50.3 (47.6–55.1) months after CyBorD, 64.5 (55–74.9) months after Rd, and NR (38.9–NR) after VRd. The median OS was 64.8 months (59.5–71.5), 51.1 months (47.7–57.6), 65.2 months (54.0–74.7), and NR (44.6–NR), respectively (Figure 2).

As mentioned, the four most used subsequent therapies were Rd, DRd, CyBorD, and VRd. The median PFS for these therapies was 18.6 (16.1–20.7), 31.9 (25.1–NR), 17.7 (12.0–25), and 14.0 (6.9–25.7) months, respectively. The median OS from the start of second-line therapy was 35.2 (32.0–38.8) for Rd, 41.0 (31.7–NR) for DRd, 47.5 (31.5–63.4) for CyBorD, and 33.3 (17.3–43.1) months for VRd. The outcomes of the other second-line regimens can be seen in Figure 3.

Given the importance of anti-CD38 monoclonal antibodies early in relapse (if not used in frontline therapy), we looked at the outcomes in patients receiving DVd and DRd, which were the regimens used before December 31, 2021. More specifically, we looked at the outcomes in patients who have received CyBorD/VMP as first-line followed by DRd (n = 142) as well as patients who received Rd as first-line followed by DVd (n = 34). In patients who received DRd in second-line after CyBorD/VMP, the median PFS was 31.9 months (26.6–NR) and median PFS2 was 71.9 months (54.7–NR). In the 34 patients who received DVd in second-line after Rd, the median PFS was 7.3 months (5.0–14.7) and median PFS2 was 43.9 months (17.0–54.8). Ninety-six patients received other bortezomib-based therapies after Rd; the mPFS is 17.7 months (10–21.2) and the mPFS2 is 39.5 months (31.7–46.9).

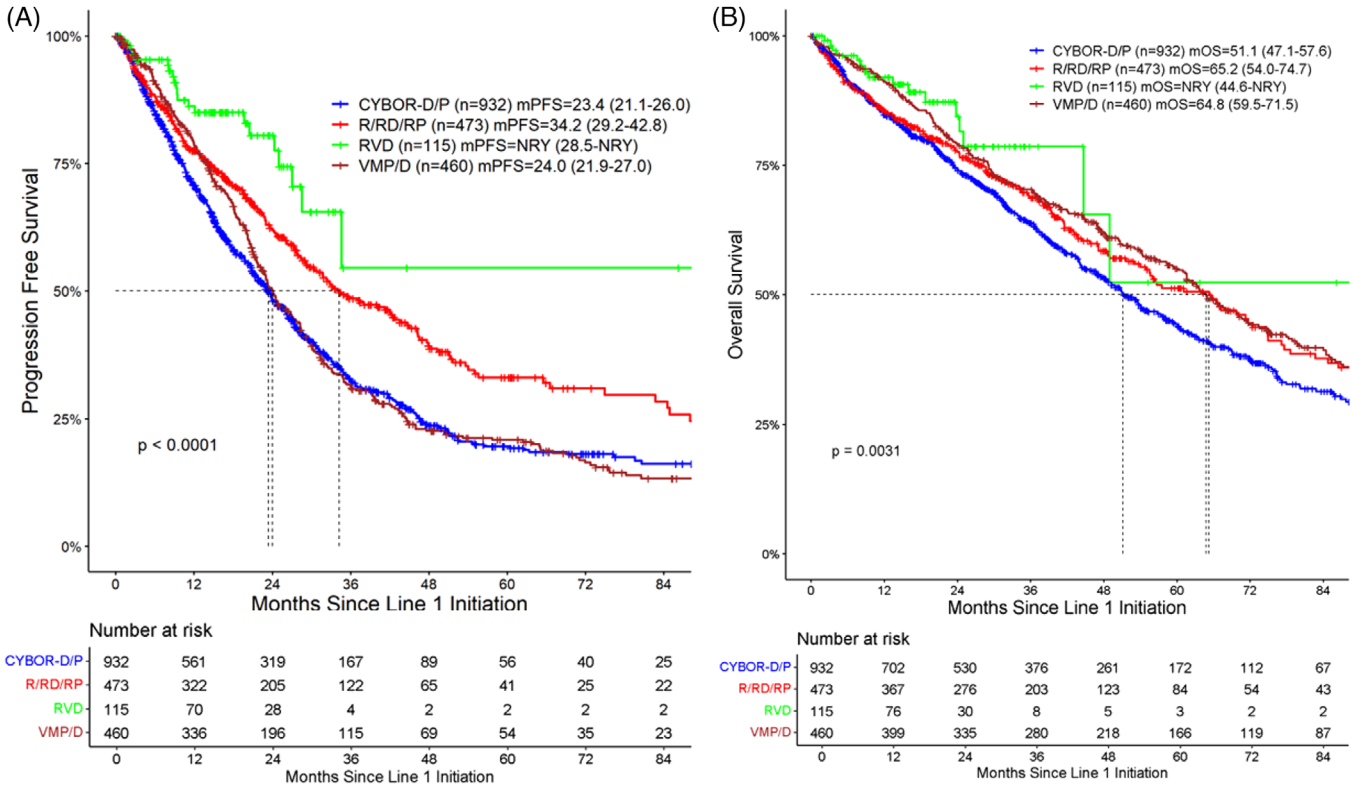

FIGURE 2 (A) Progression-free survival (PFS) by line 1 treatment and (B) overall survival (OS) by line 1 treatment.

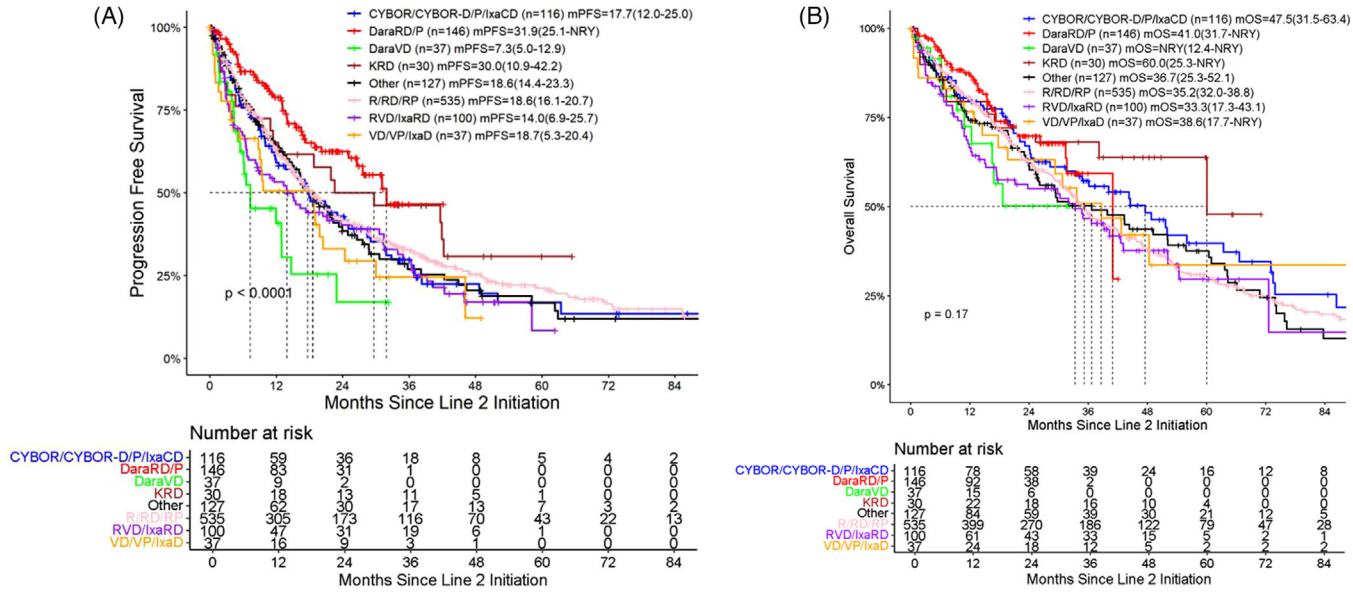

FIGURE 3 (A) Progression-free survival (PFS) for second-line therapy and (B) overall survival (OS) for second-line therapy.

3.2 | Multivariable analysis

From our multivariable analysis (MVA), factors associated with a worse PFS with front-line therapy included older age, high LDH, and an ISS 3. Factors associated with more favorable PFS, PFS2, and OS were receiving VRd or Rd in the front line and standard risk cytogenetics. Age, ISS, and LDH were also associated with worse OS in the MVA. Having received DRd in second-line as well as having standard risk cytogenetics are associated with a statistically significantly superior PFS2. (Figure 4)

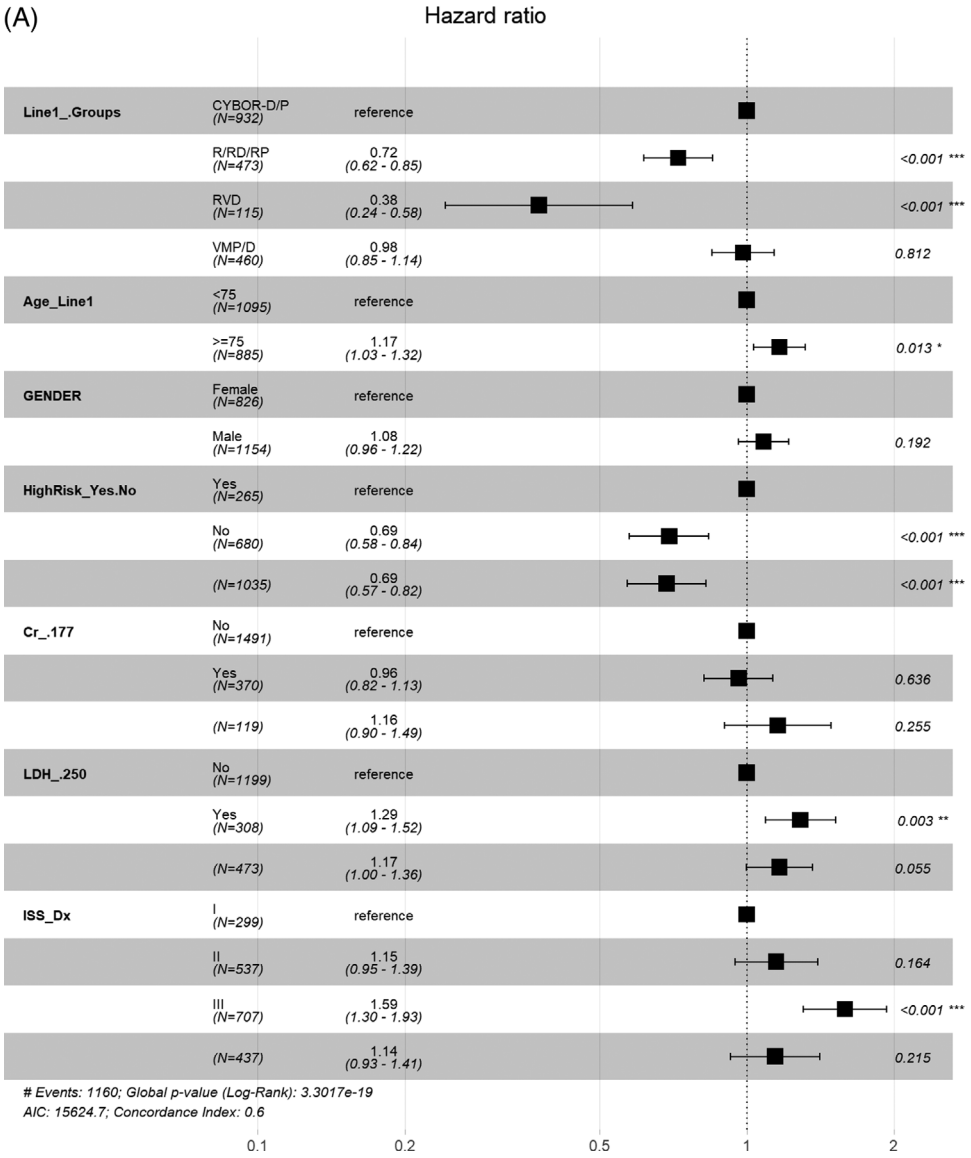

FIGURE 4 Multivariable Analysis forest plot for factors associated with (A) Line1_Progression-free survival (PFS), (B) overall survival (OS), and (C) PFS2.

4 | DISCUSSION

Herein, we present an update on response and survival outcomes among patients with TIMM in the CMRG registry. While the integration of anti-CD38 monoclonal antibodies into frontline therapy is now considered standard of care, its routine use is relatively new such that the cohort presented here better reflects the type of TIMM patient currently experiencing relapse in real-world settings. In our previous report on outcomes among TIMM patients, we focused on four induction regimens including CyBorD, VMP, Vd, and Rd. With this update, we have removed Vd and added VRd, to reflect changing practice patterns. In addition, we include survival data on second-line therapy as well as PFS2. When DRd in second-line became approved in Canada, questions pertaining to sequencing and whether the use of lenalidomide should be adjusted in order to use it in combination with second-line given the positive results of the POLLUX trial. These results demonstrate that the use of Rd upfront did not negatively impact the PFS2 in the entire cohort, thus supporting the notion of using what is felt to be the best regimen upfront. Notably, the attrition rate due to death described here is consistent with other analyses within our database as well [11]. The longer follow-up in this series allows for the assessment of outcomes from second-line therapy and to compare these results with the prospective phase 3 trial data that have shaped current practice in this setting. It is well known that the generalizability of phase 3 trials in MM is compromised by rigorous eligibility criteria, which often do not match many patients encountered in real-world practice [12].

In the front-line setting, although CyBorD resulted in higher and deeper ORR, these responses were not durable, likely due to the fact that the therapy was finite in nature. As previously reported in our last

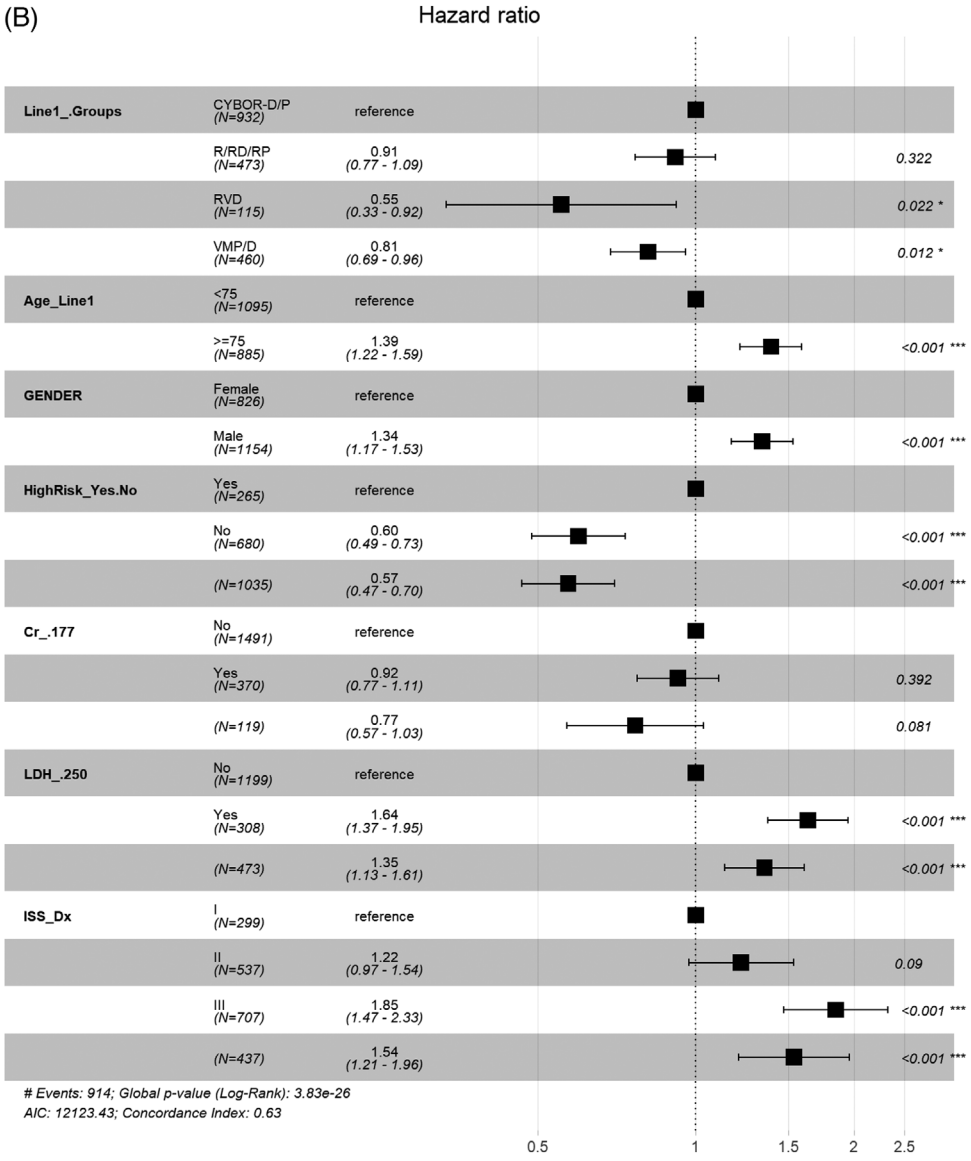

FIGURE 4 Continued

publication, CyBorD and VMP provided equivalent PFS benefits. Rd had the longest statistically significant PFS and our results are more comparable to the PFS outcomes in the control arm of MAIA rather than the FIRST trial, demonstrating that a clinician's familiarity with a regimen and more flexible dose adjustments likely have an impact on outcomes. It is to be noted, that although this regimen was intended to be given until progression, the median duration of time on therapy was 12.3 months. The main reasons for discontinuation included progressive disease (36.2%) and toxicity (14.4%). In the second-line setting, the most common regimen prior to the approval of daratumumab in our cohort was Rd. This is likely due to the longstanding and widespread use of BCR in the frontline setting. Our results compare favorably to phase 3 trials where Rd was the comparator arm. For example, in looking at the first relapse subgroup in the phase 3 study POLLUX [13] the median PFS in the Rd arm was 19.6 months. Similarly, in the ASPIRE trial [14], comparing KRd to Rd, the Rd arm PFS was 17.6 months in the first relapse space. In our study, the PFS for Rd was 18.6 months.

Our results highlight the superiority of anti-CD38 monoclonal antibodies in combination with Rd in second-line therapy. Nevertheless, our median PFS with DRd was less impressive than that seen in the second-line setting in the phase 3 POLLUX trial (31 months vs. 53.3 months) [15]. However, our patients were older and had not received prior stem cell transplantation. In POLLUX, nearly 50% of patients were under the age of 65 with only 10% of patients being older than 75. In the subgroup analysis of POLLUX by age, the median PFS of patients > 75y was 28.9 months [16]. Although it may appear that receiving DRd after a CyBorD/VMP is an optimal sequence based on the long PFS2 seen in this group in our study, this result is mainly driven by a small number of patients that had a longer time to next

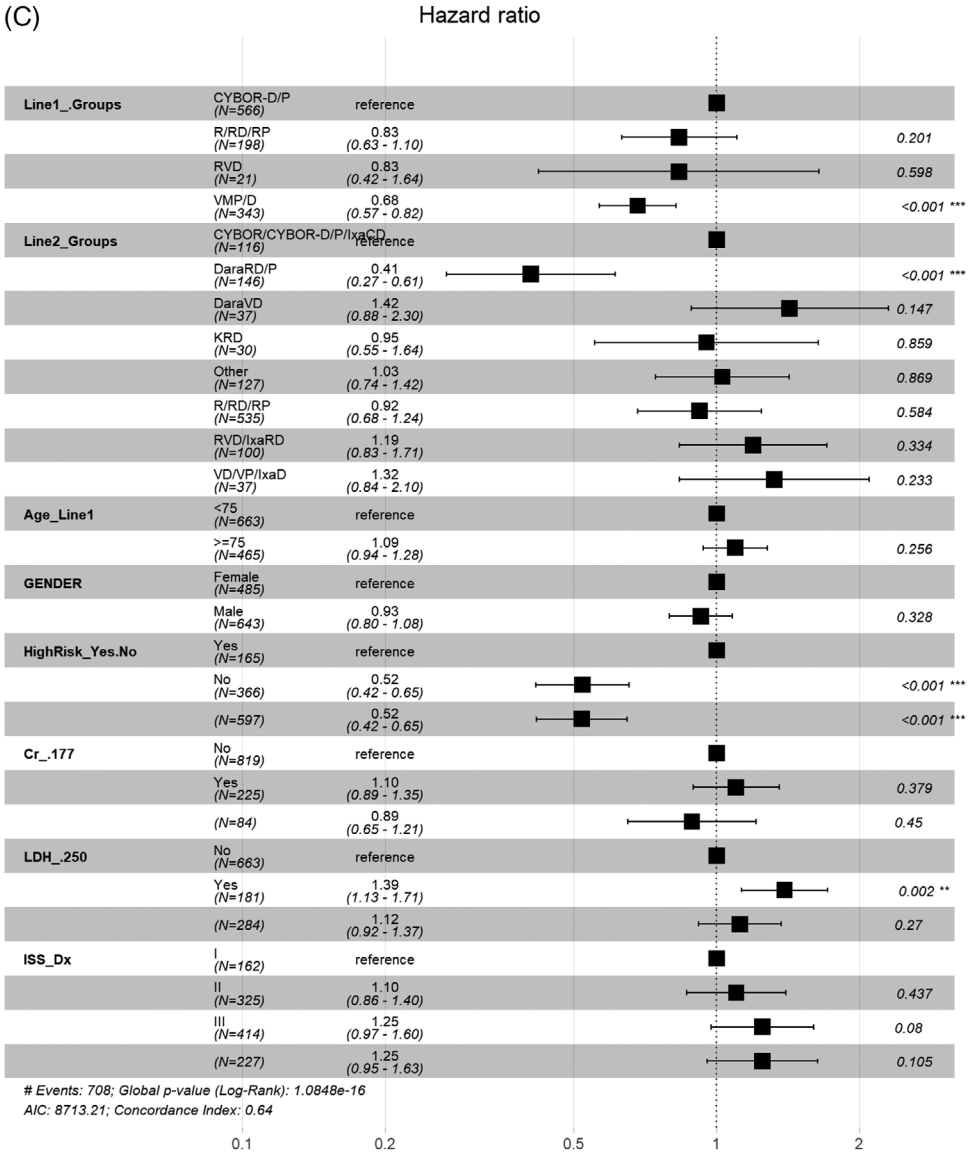

FIGURE 4 Continued

treatment after initial therapy. These results need to be interpreted in that context, as using DRd in the front-line setting is based on the large phase 3 MAIA trial.

The number of patients treated with other regimens in the second-line setting becomes quite small but, interestingly, patients treated with KRd ($n = 30$) fared well and had similar PFS to the patients treated with DRd. There may have been a physician selection bias toward choosing KRd for patients with a better performance status, given the toxicities associated with carfilzomib. Carfilzomib-based therapy in second-line was rare in the database with only 8 patients having received Kd or KCd in second-line treatment. These regimens were more often used beyond second-line due to funding algorithms that may have precluded the use of anti-CD38 treatments should patients be refractory to both IMiDs and proteasome inhibitors.

As described in the literature, patients progressing after frontline Rd appears to be a higher risk group. While there are no phase 3 trials evaluating CyBorD or IxaCd in second-line after lenalidomide refractoriness, certain phase 2 trials in the early relapse space have shown similar outcomes to what is reported here (median PFS of 17.7months), however, the number of lenalidomide refractory patients included is not clear in these studies [17]. In the phase 3 CASTOR trial [18], looking at the combination of DVd versus Vd in relapsed MM patients, although the number of lenalidomide refractory patients was small, the outcomes were also less than 12 months in the small subgroup, highlighting the high-risk nature of these patients. As mentioned in the results section, it is interesting to see that patients receiving bortezomib-based therapies other than DVd do better. This can perhaps be explained by the way that these regimens were being given. In general, patients on bortezomib-based therapies other than DVd were receiving continuous PI therapy as compared to patients on DVd who only received 8 cycles of bortezomib with daratumumab maintenance as per the CASTOR trial.

4.1 | Limitations

Our study carries the limitations inherent to any retrospective analysis. As this is not a randomized trial, the selection of therapy is at the discretion of the physician, and in the front-line setting, more patients with high-risk disease and renal dysfunction were put into BCR to induce a more rapid response and to avoid dose adjustments and toxicities associated with giving lenalidomide to patients with renal impairment. We did not capture dose reduction and modifications that could have impacted outcomes and toxicities were not formally assessed, limiting the ability to weigh the risks and benefits of the frontline regimens assessed here.

5 | CONCLUSIONS

This real-world data set of almost 2000 patients treated in the frontline before the widespread use of daratumumab demonstrates that both response rates and survival are concordant with clinical trials using these regimens. The long follow-up of this study also allows for the analysis of outcomes after second-line therapy. Prior to the approval of DRd in the frontline setting for TIMM patients in Canada, the issue of whether to "save" lenalidomide for use at relapse, in order to be able to combine it with daratumumab, was often raised. This study provides reassurance that OS is comparable whether lenalidomide is used upfront or in the relapse setting. This finding supports the approach of selecting a frontline therapy that is best suited for the patient at that moment in their myeloma trajectory. Our results remain pertinent for jurisdictions where expensive triplets that include daratumumab may not be accessible in the frontline setting. As well, we demonstrate that daratumumab in the second-line setting results in inferior outcomes when given to an older patient population, suggesting that greater vigilance and care may be required to ensure favorable outcomes in older patients. ND-TIMM patient outcomes are improving with earlier use of novel therapeutics. However, this is at the cost of becoming refractory to more classes earlier on. In the future, we hope to be able to report on the RWE with the use of more novel therapeutics such as bispecific antibodies and chimeric antigen receptor T in this more vulnerable and fragile patient population.

AUTHOR CONTRIBUTIONS

Rayan Kaedbey drafted the original manuscript and incorporated all of the revisions of the group. Major contributions from Christopher P. Venner, Hira Mian, Richard LeBlanc, Jiandong Su, Donna Reece, and Michael Sebag—All authors provided feedback and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Kaedbey: Honoraria: Janssen, BMS, FORUS, Sanofi, and Pfizer. **Reece**: Research funding: Janssen, Takeda, BMS, and Millennium; Consultancy: Janssen, Amgen, Takeda, and BMS; Honoraria: BMS, Janssen, Takeda, Sanofi, Pfizer, and GSK. **Venner**: Honoraria: Janssen, BMS, Pfizer, Abbvie, Sanofi, Forus, and GSK. **McCurdy**: Honoraria: Celgene, Janssen, Amgen, Takeda, Sanofi, and GSK. **Chu**: Honoraria: AstraZeneca, BMS/Celgene, Gilead, Janssen, AbbVie, Pfizer, Sanofi, and Amgen; Research funding: BMS/Celgene and Miltenyi. **Louzada**: Honoraria: Janssen, Celgene, Amgen, and Pfizer. **Jimenez-Zepeda**: Honoraria: Celgene, Janssen, Takeda, Merck, and BMS. **Mian**: Honoraria: Celgene, Janssen, Amgen, Takeda, Sanofi, and GSK Awards: HHS Research Early Career Award from Hamilton Health Sciences Foundation. **Song**: Honoraria: Janssen, Sanofi, BMS, Forus, Amgen, GSK, Gilead, and Novartis. **Sebag**: Membership on an entity's Board of Directors or advisory committees: Janssen Inc., Amgen Canada, Takeda Canada, and Celgene Canada. **Stakiw**: Honoraria: Janssen, FORUS Therapeutics, Pfizer, and Sanofi. **White**: Honoraria: Amgen, Antengene, BMS, Forus, GSK, Janssen, Karyopharm, Pfizer, Sanofi, and Takeda. **Reiman**: Consulting/honoraria/research: Janssen, Sanofi, BMS, Takeda, Pfizer, Regeneron, and AstraZeneca. **Aslam**: Honoraria: AbbVie, Gilead, Janssen, and Celgene. **Bergstrom**: Honoraria: Janssen and BMS. Research funding: BMS. **Kotb**: Honoraria: Akcea, Amgen, BMS, Janssen, Merck, Sanofi, Celgene, Pfizer, and Takeda; Research funding: Merck and Sanofi; Current equity holder in a private company: Karyopharm. **LeBlanc**: Advisory committees: BMS, Janssen, Amgen, Sanofi, and FORUS Therapeutics; Honoraria: Pfizer

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

ETHICS STATEMENT

Entry of source data into the CMRG-DB is approved by local research ethics boards at every contributing site. The approval for review of this specific dataset was obtained from the Jewish General Hospital institutional review board as per the approved governance structure of the CMRG-DB and in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

Patients consented to have their data collected within the structure of the CMRG database and are aware that the data is to be used to evaluate real-world treatment outcomes.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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