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REVIEW

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Lenalidomide, bortezomib and dexamethasone induction therapy for the treatment of newly diagnosed multiple myeloma: a practical review

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Summary

For patients with newly diagnosed multiple myeloma, survival outcomes continue to improve significantly: however, nearly all patients will relapse following induction treatment. Optimisation of induction therapy is essential to provide longer term disease control and the current standard of care for most patients incorporates an immunomodulatory agent and proteasome inhibitor, most commonly lenalidomide and bortezomib in combination with dexamethasone (RVD), with maintenance until progression. Historically there has been limited access to RVD as an induction strategy outside of the United States; fortunately, there is now increasing access worldwide. This review discusses the rationale for use of RVD as induction therapy and aims to provide guidance in prescribing this regimen in order to optimise efficacy while minimising the toxicities of treatment. We also highlight the increasing evidence for the utility of addition of a monoclonal antibody to the RVD backbone to deepen responses and potentially provide longer disease control.

INTRODUCTION

Lenalidomide, bortezomib and dexamethasone (RVD, sometimes used interchangeably with the acronym VRD, although originally this was used to describe a different regimen detailed below) is the preferred induction regimen for most patients with newly diagnosed multiple myeloma (NDMM). This combination has been demonstrated in Phase I/II and III studies to be associated with excellent response rates and manageable toxicities as well as clinical benefit.[1–8] The pivotal Phase III Southwest Oncology Group (SWOG) S0777 study also demonstrated significantly improved progression-free (PFS) and overall survival (OS) compared to lenalidomide/dexamethasone (Rd) alone in a newly diagnosed patient population with no immediate intent to proceed to autologous stem cell transplantation (ASCT)[1] (Figure 1).

It may seem counterintuitive to combine lenalidomide and bortezomib therapy given that lenalidomide-mediated degradation of Ikaros family members, IKZF1 and IKZF3, occurs via a proteasome-dependent pathway.[9,10] However, prior to the full elucidation of this mechanism preclinical and clinical synergy had already been demonstrated between the two agents, with efficacy in clinical trials seen both in the newly diagnosed and relapsed, refractory setting.[4,11,12] Mechanisms for the synergistic effects have been proposed including incomplete proteasome blockade by bortezomib[9] and non-proteasome-dependent degradation of IKZF1, as well as recently described immunogenic cell death associated with bortezomib use.[13,14]

There is increasing access worldwide to RVD as induction therapy for NDMM and this review aims to provide practical guidance regarding the use of lenalidomide, bortezomib and dexamethasone in newly diagnosed patients, including
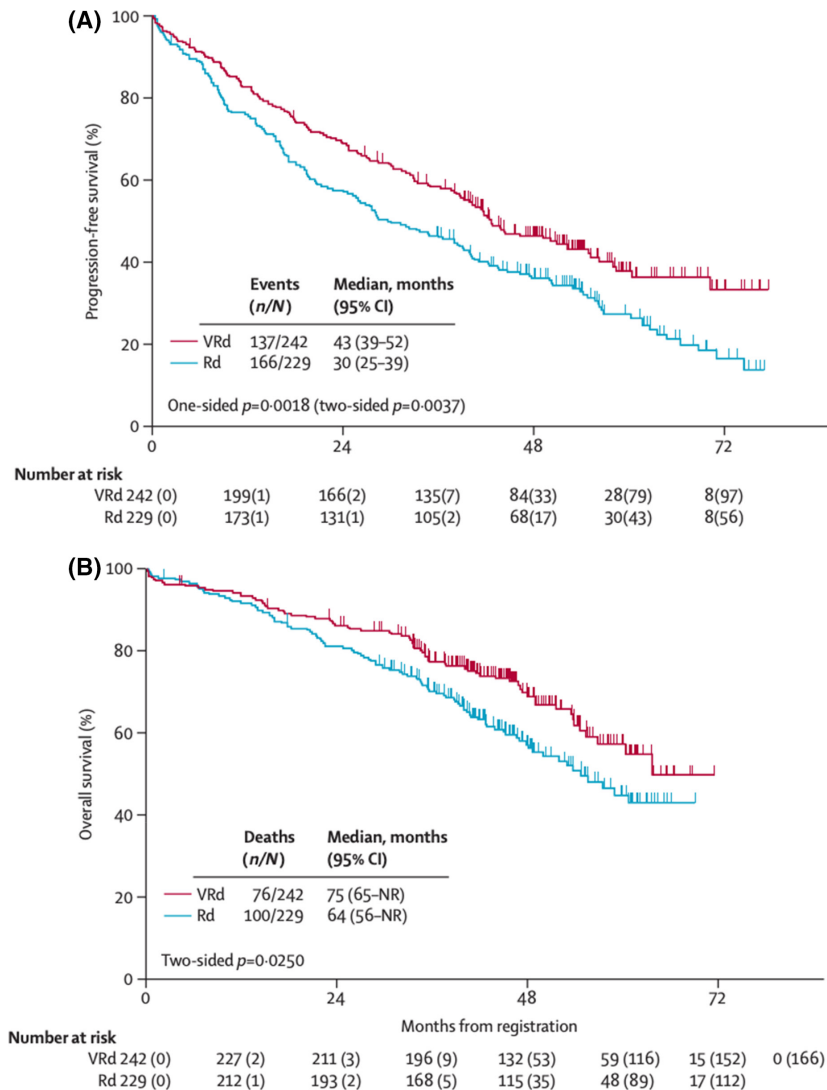
FIGURE 1 Kaplan–Meier estimates of progression-free survival and overall survival comparing VRd versus Rd in SWOG S0777.[1] CI, confidence interval; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

the different dosing approaches and the management of common toxicities.

WHAT IS THE EVIDENCE FOR THE TRANSPLANT-ELIGIBLE PATIENT?

RVD induction therapy prior to planned ASCT has been evaluated in Phase II and Phase III studies.[2,6–8,15] A subset of patients in other studies have also undergone up-front ASCT.[4,5] After induction, a very good partial response or better (≥VGPR) is seen in 45%–67% of patients,[2,6–8] increasing post-ASCT ≥VGPR to rates of 66%–75%. Further improvement is possible with consolidation and maintenance therapy.[2,6,8,16] The median PFS in the IFM 2009 study, which compared RVD induction followed by ASCT with RVD alone, was 47.3 months in the transplantation arm compared to 35 months in those who did not undergo

up-front ASCT.[2,17] However, there was no significant difference in OS at 8 years, at 62.2% and 60.2% respectively.[2] In 1000 consecutive patients treated with RVD induction at Emory University, 751 underwent up-front ASCT and in this cohort the median PFS was 63 months and median OS was 123.4 months.[16] In this study, a selected group of 168 patients who had standard-risk disease and a good response to induction therapy were offered deferred ASCT. The median PFS of this group was 74.3 months and median OS was not reached at a median follow-up of 102 months.[16]

Apart from the EVOLUTION study, RVD has not been formally compared to induction strategies previously used prior to ASCT, such as bortezomib/cyclophosphamide/dexamethasone (VCD) or bortezomib/thalidomide/dexamethasone (VTD).[5] A comparison of the different induction regimens is found in Table 1. Of note, in the EVOLUTION study, the dexamethasone was administered weekly and

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TABLE 1 Comparison of available induction regimens

	Key trials	Efficacy, %	Notable adverse effects, %
Newly diagnosed, transplant eligible			
Bortezomib, lenalidomide, dexamethasone (RVD)	PETHEMA/GEM 2012[7,18] ENDURANCE GRIFFIN[8] SWOG S0777[1,19,20]	Post-induction[a] ORR 81.5–92 ≥VGPR 45–67	Post-induction[a] Grade ≥3 Peripheral neuropathy: 3.9–33[b] Grade ≥3 Neutropenia: 12.9 Grade ≥3 Thrombocytopenia: 6.3
Bortezomib, thalidomide, dexamethasone (VTD)	IFM 2013-04[99] CASSIOPEIA[21]	Post induction[a] ORR 89.9–92.3 ≥VGPR 66.3–78 IFM 2013-04 demonstrated improved response rates compared to VCD[22]	Post-induction[a] Grade ≥3 Peripheral neuropathy: 7.7[b] Grade ≥3 Neutropenia: 10–15 Grade ≥3 Thrombocytopenia: 7–8
Bortezomib, cyclophosphamide, dexamethasone (VCD/CyBorD)	Reeder et al.[23] IFM 2013-04[99]	Post-induction[a] ORR 83.4–88 ≥VGPR 56.2–61	Post-induction[a] Grade ≥3 Peripheral neuropathy: 2.9–7[b] Grade ≥3 Neutropenia: 13–33.1 Grade ≥3 Thrombocytopenia: 10.6–25
Carfilzomib, lenalidomide, dexamethasone (KRd)	ENDURANCE[20] FORTE[24] (abstract only) IFM KRd[25]	Post-induction[a] ORR 87 ≥VGPR 74 ENDURANCE did not demonstrated superiority over VRD induction in patients without intent for immediate transplantation	Post-induction[a] Grade ≥3 Cardiac toxicity: 6 Grade ≥3 Renal toxicity: 4 Grade 4 Neutropenia: 2 Grade 4 Thrombocytopenia: 1
Daratumumab, bortezomib, thalidomide, dexamethasone (Dara-VTd)	CASSIOPEIA[84]	Post-induction[a] ORR 92.7 ≥VGPR 65 CASSIOPEIA demonstrates response rates and PFS compared to VTD	Induction and consolidation Grade ≥3 Peripheral neuropathy: 9 Grade ≥3 Neutropenia: 28 Grade ≥3 Thrombocytopenia: 11
Newly diagnosed, transplant ineligible			
Bortezomib, lenalidomide, dexamethasone	SWOG S0777[1,19] RVD Lite[3]	ORR 81.5–86 ≥VGPR 43.5–66 SWOG S0777 demonstrated improved PFS and OS compared to lenalidomide/dexamethasone	SWOG S0777, Grade ≥3 Neurological events: 33 RVD Lite, Grade ≥3 Peripheral neuropathy 2 SWOG S0777: Grade ≥3 Blood or bone marrow adverse events: 47 RVD Lite, Grade ≥3 Neutropenia: 14 RVD Lite, Grade ≥3 Thrombocytopenia: 2
Bortezomib, cyclophosphamide, dexamethasone	Reeder et al.[23]	ORR 88 ≥VGPR 61	Grade ≥3 Neuropathy: 7 Grade ≥3 Neutropenia: 13 Grade ≥3 Thrombocytopenia: 25
Bortezomib, dexamethasone	Jagganath et al.[99]	ORR 88	Grade ≥3 Neuropathy: 16 Grade ≥3 Neutropenia: 16 Grade ≥3 Thrombocytopenia: 3
Lenalidomide, dexamethasone	FIRST[100,101] SWOG S0777[1,19] MAIA[102]	ORR 71.5–81.3 ≥VGPR 31.8–53 FIRST demonstrated lenalidomide/dexamethasone is superior with regards to PFS to fixed duration lenalidomide/dexamethasone and melphalan/prednisone/thalidomide and superior OS compared to melphalan/prednisone/thalidomide	Grade ≥3 Neutropenia: 28–35.3 Grade ≥3 Thrombocytopenia: 8 Grade ≥3 Infections: 23.3–29 Grade ≥3 DVT: 8

TABLE 1 (Continued)

	Key trials	Efficacy, %	Notable adverse effects, %
Daratumumab-lenalidomide-dexamethasone (DaraRd)	MAIA[27,101]	ORR 92.9 ≥VGPR 79.3 MAIA demonstrated DaraRd had a superior OS and PFS to Rd	Grade≥3 Neutropenia: 54 Grade≥3 Infections: 41 Grade≥3 Pneumonia: 19 Grade≥3 Infusion-related reaction: 2.7
Daratumumab-bortezomib-melphalan-dexamethasone	ALCYONE[77,83]	ORR 91 ≥VGPR 73 ALCYONE demonstrated superiority of Dara-VMP over VMP with regards to PFS and OS	Grade≥3 Peripheral neuropathy: 1.4 Grade≥3 Neutropenia: 39.9 Grade≥3 Thrombocytopenia: 34.4 Grade≥3 Infections: 23.1 Grade≥3 Pneumonia: 11.3 Grade≥3 Infusion reaction: 4.9

Abbreviations: DVT, deep venous thrombosis; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; ≥VGPR, very good partial response or better.

aPost-induction response rates and induction related toxicity not reported for all studies.

bVariable between schedules with different number of cycles, intravenous versus subcutaneous administration of bortezomib.

not partnered with bortezomib but rather aligned according to the lenalidomide/dexamethasone regimen (hence VRD rather than RVD), and this may explain the lower response rates and higher rates of peripheral neuropathy seen with this regimen in this study.[5,26] A cross trial comparison of GEM 2012 and GEM 2005 demonstrated statistically significant improvement in post-induction and post-ASCT ≥VGPR rates with the use of six cycles of RVD compared to six cycles of VTD.[27] Of note, higher rates of Grade 3/4 haematological toxicities were seen with RVD compared with VTD but significantly lower rates of peripheral neuropathy were noted. Despite the limited number of direct comparisons of RVD to other induction strategies in the transplant-eligible population, the totality of evidence reflected by improved response rates and manageable toxicities, as well as clinical benefit, RVD has become a standard of care for induction therapy for most transplant-eligible patients with MM. However, it must be noted that many healthcare systems do not have access to this induction strategy, and here other regimens including VTD and VCD are extensively used.

Recent data from the GRIFFIN and GMMG-HD7 studies adding a CD38-directed monoclonal antibody (mAb) to a RVD backbone have demonstrated an improvement in response rates and minimal residual disease (MRD)-negative rates in patients considered transplant eligible.[8,28] Neither of these studies were powered to examine PFS or OS, nonetheless GRIFFIN has recently demonstrated a significant PFS benefit with the four drug combination.[29] Quadruplet induction incorporating a CD38 mAb may therefore become the standard of care in patients with myeloma who are considered transplant eligible.

RVD chemotherapy combinations are a rationale choice for plasma cell leukaemia; however, the data supporting the use of these regimens is heterogenous and limited.[5,30] In the era of monoclonal antibodies, a CD38-directed mAb, or alternatively venetoclax given the high rate of t(11;14) in combination with RVD represent attractive options.[30]

WHAT IS THE EVIDENCE FOR THE TRANSPLANT-INELIGIBLE PATIENT?

The SWOG S0777 study randomised newly diagnosed patients who had no immediate intent for ASCT to either eight cycles of RVD induction followed by continuous Rd or continuous Rd. PFS and OS were significantly improved in patients who received RVD induction, and the median OS in the RVD group has not been reached at 84 months of follow-up, compared to 69 months in the Rd group[19] (Figure 1). Only 43% of patients were aged ≥65 years and it may be argued that this limits its applicability to a truly transplant-ineligible patient cohort. The benefits with regards to PFS and OS did appear to extend to patients aged ≥65 years in this study, albeit not reaching statistical significance in this subset with regards to OS (hazard ratio 0.79, 95% confidence interval [CI] 0.520–1.138, $p = 0.168$).[19]

In all, 23% of patients receiving RVD in this study discontinued therapy due to adverse events, and less intensive regimens with longer cycle length and dose attenuation have been proposed, in particular for older patients.[3] Specifically, RVD Lite demonstrated a VGPR rate of 66% and a median PFS of 41.9 months, which is comparable to 41 months in the updated analysis of the SWOG S0777 study.[3,19] A recent network meta-analysis simultaneously assessing the comparative efficacy of several treatment options by direct and indirect comparisons showed that RVd was the only therapy with evidence of superiority over Rd in terms of OS.[31] Table 1 provides a summary of different induction regimens in the transplant-ineligible patient.

Regimens incorporating daratumumab in transplant-ineligible patients have demonstrated improved OS compared to bortezomib/melphalan/prednisone (VMP) and Rd backbones.[32,33] In ALCYONE, the addition of daratumumab to VMP (D-VMP) resulted in a 3-year OS of 78% (95% CI 73.2–82.0) compared to 67.9% (95% CI 62.6%–72.6%) in the VMP arm.[33] A PFS of 36.4 months (95% CI 32.1–45.9) with D-VMP versus 19.3 months (95% CI 18.0–20.4) with VMP. In

MAIA, daratumumab-Rd (DRd) had a 60 month OS of 66.3% (95% CI 60.8%–71.3%) compared to 53.1% (95% CI 47.2%–58.6%) in the Rd arm and a median follow-up of 56.2 months, median PFS was not reached in the DRd arm and was 34.4 months in the Rd arm.[32] D-VMP has not been directly compared to RVD and data comparing DRd and RVD or a quadruplet incorporating a mAb with RVD in the transplant-ineligible population are not yet available. Of note, there is an ongoing study comparing DRd to RVD Lite and another comparing Dara-RVD with RVD in this population.[34]

WHAT DOSING AND SCHEDULE SHOULD I USE IN A TRANSPLANT-ELIGIBLE PATIENT?

Cycle length and dosing schedules have varied across trials utilising up-front ASCT (Table 2). All these studies utilised day 1, 4, 8, 11 bortezomib dosing, and the later studies utilised subcutaneous bortezomib given the lower risk of peripheral neuropathy with this route of administration.[35] Retrospective analysis of patient level data from three Phase III studies demonstrated that weekly dosing of bortezomib (in combination with melphalan and prednisone) was associated with a lower risk of toxicity, specifically peripheral neuropathy[36] and using this strategy warrants consideration, in particular in patients who may not require more rapid disease control. Of note, a small retrospective analysis of 48 patients by Okazuka et al.[15] utilising weekly bortezomib in a 28-day cycle prior to planned ASCT demonstrated a ≥VGPR rate after induction of 48%, which is comparable to the published Phase II and III studies utilising day 1, 4, 8, 11 dosing. A number of RVD schedules have been proposed including RVD Classic, RVD Lite and RVD Premium Lite to minimise toxicity, which are detailed in Table 3. Higher bortezomib doses, up to 1.5–1.6 mg/m^2 are sometimes utilised in weekly protocols[37,38] to facilitate more convenient clinical visits and optimise dose intensity. If this approach is being utilised, the administration of intravenous normal saline may be helpful to minimise neurotoxicity and fatigue.[39]

The optimal number of cycles of RVD prior to ASCT remains to be defined with most clinicians utilising three to six cycles. A balance between obtaining best response and toxicity is advisable. In the Phase III PETHEMA/GEM 2012 study, which utilised six 28-day cycles, response rates continued to improve during induction, with a ≥VGPR rate of 55.6% after three cycles and 66.6% after six cycles. Extending the number of induction cycles beyond four in those who have not yet achieved best response may be prudent; moreover, there may also be a benefit in those who have achieved a VGPR in terms of pursuing MRD negativity. Specifically, analysis of patients enrolled in the PETHEMA/GEM 2012 study demonstrated that achievement of MRD negativity overcame the poorer prognosis of patients with high-risk cytogenetics.[40] There is no available evidence that prolonging induction beyond six cycles pre-ASCT results in significant deepening of response and cumulative toxicity needs to be considered, but this is an approach adopted when ASCT is not being immediately pursued and in this context between eight and 12 cycles are typically used.[33,37]

An ASCT deferral remains a reasonable alternative given the equivalent median OS between the up-front and delayed ASCT arms in the IFM 2009 study.[2,17] Up-front ASCT was associated with a significantly better median PFS of 47.3 months compared with 35 months in the delayed transplant arm;[17] however, the increased mutational burden following high-dose melphalan, which may alter disease behaviour at relapse, has to be taken into account.[41] A further consideration is that 76.7% of patients in the delayed transplant arm of IFM-2009 underwent ASCT after re-induction, which may be higher than in a real-world population. There was no significant difference in PFS2 between both treatment arms reflecting the efficacy of salvage treatment.[17]

The optimal number of induction cycles of RVD in patients in whom transplant is deferred is not known. In the IFM 2009 study,[17] eight 21-day cycles were used, with a ≥VGPR of 77% and median PFS of 36 months, while the ENDURANCE study utilised 12 21-day cycles with a ≥VGPR of 65% and median PFS of 34.4 months.[20] In the FORTE study, 12 cycles of KRd induction were utilised in patients in

TABLE 2 Bortezomib, lenalidomide, dexamethasone (RVD) Phase II and III studies with planned up-front autologous stem cell transplantation

	Patients, n	Cycle length, days	Induction cycles, n	Consolidation cycles, n	Bortezomib	Lenalidomide	Dexamethasone
Roussel et al. 2014[6]	31	21	3	2	IV 1.3 mg/m^2 Day 1, 4, 8, 11	25 mg Day 1–14	40 mg Day 1, 8 and 15
Attal et al. 2017[2]	350	21	3	2	IV 1.3 mg/m^2 Day 1, 4, 8, 11	25 mg Day 1–14	20 mg[a] Day 1, 2, 4, 5, 8, 9, 11, 12
Rosinol 2019[7]	458	28	6	2	SC 1.3 mg/m^2 Day 1, 4, 8, 11	25 mg Day 1–21	40 mg Day 1–4 and 9–12
Voorhees et al. 2020[8]	103	21	4	2	SC 1.3 mg/m^2 Day 1, 4, 8, 11	25 mg Day 1–14	20 mg Day 1, 2, 8, 9, 15, 16

Abbreviations: IV, intravenous; SC, subcutaneous.

[a]During consolidation in Attal et al.[2] dexamethasone was dosed at 10 mg.

TABLE 3 Modified bortezomib, lenalidomide, dexamethasone (RVD) protocols

Protocol name	Cycle length, days	Bortezomib	Lenalidomide	Dexamethasone
RVD classic	21	SC 1.3 mg/m² Day 1, 4, 8, 11	25 mg Day 1–14	Day 1, 2, 4, 5, 8, 9, 11, 12
RVD lite	35	SC 1.3 mg/m² Day 1, 8, 15, 22	15 mg Day 1–21	Day 1, 2, 8, 9, 15, 16, 22, 23
RVD premium lite	28	SC 1.3 mg/m² Day 1, 8, 15, 22[a]	15–25 mg Day 1–21[b]	Day 1, 2, 8, 9, 15, 16, 22, 23
RVD ultra lite	28–35	SC 1.3 mg/m² Day 1, 8, 15	15 mg Day 1–21[b]	Day 1, 2, 8, 8, 15 and 16

Abbreviation: SC, subcutaneous.

[a]Bortezomib dose can be increased to 1.5–1.6 mg/m².

[b]Active doses of lenalidomide range from 5–25 mg, dose can be modified according to patient factors such as frailty and toxicity.

whom transplant was deferred providing a rationale of prolonged induction in the setting of transplant deferral.[42]

In practice, we prescribe a classical 21-day RVD protocol (Table 3) in selected younger patients with higher-risk disease. In most transplant eligible patients, we prescribe a 28-day cycle (RVD Premium Lite, Table 3) utilising weekly bortezomib in an attempt to minimise toxicity while maintaining efficacy. In some patients we consider an increased dose of bortezomib (1.5–1.6 mg/m²) to facilitate more convenient clinical visits and optimise dose intensity.

We aim to achieve at least a partial response before proceeding with ASCT. As a minimum, we administer four cycles of induction therapy and consider an additional two cycles in patients demonstrating an on-going response to therapy and who have not achieved a VGPR. If the patient has not achieved a partial response at the completion of cycle four, we proceed with stem cell mobilisation and collection, and then the treatment approach varies significantly between healthcare systems depending on access to salvage regimens. Therapeutic options that we consider in the setting of suboptimal response to RVD induction include addition of a mAb (daratumumab, isatuximab, elotuzumab) to the RVD backbone, change of regimen or access to novel agents through clinical trial involvement.

Up-front quadruplet therapy incorporating a mAb is not available in many healthcare systems. However, RVD in combination with daratumumab is becoming increasingly used as up-front treatment in most patients in the United States.

In those patients in whom a deferred ASCT approach is adopted, we administer up to 12 cycles of RVD induction therapy depending on clinical response and toxicities of therapy, noting that this duration of therapy is not available in all healthcare systems.

WHEN AND HOW SHOULD I MOBILISE STEM CELLS IN A PATIENT RECEIVING LENALIDOMIDE, BORTEZOMIB AND DEXAMETHASONE?

It is critical in the management of transplant-eligible patients to mobilise and collect an adequate quantity of CD34⁺

stem cells, at a minimum of 2×10^6 CD34⁺ cells/kg. Due to the potential impact of lenalidomide on stem cell mobilisation[43] and to avoid mobilisation failure, we advocate performing stem cell mobilisation after completion of no more than four cycles of induction. If using a 28-day cycle, mobilisation after the third cycle should be considered as per the GEM 2012 study.[7]

There is institutional and geographical variation in mobilisation technique that varies depending on institutional experience and access to plerixafor. In practice, we proceed with stem cell mobilisation ~6 weeks after day 1 of cycle three or four utilising granulocyte colony-stimulating factor (G-CSF) alone or in addition to high-dose cyclophosphamide depending on institutional and geographical preferences. All the published studies, apart from GRIFFIN,[8] utilised cyclophosphamide mobilisation. GRIFFIN only allowed cyclophosphamide mobilisation if the patient failed filgrastim ± plerixafor (≤5.3%), and 56.4% of patients received plerixafor. This strategy may not be appropriate in jurisdictions where there is limited access to plerixafor, or if plerixafor access is restricted to patients in whom cyclophosphamide mobilisation has failed.

Decisions regarding timing of mobilisation were previously made based on concern regarding impaired mobilisation with protracted lenalidomide therapy; however, in practice mobilisation can be achieved after multiple cycles of RVD induction therapy provided the patient has had a break off treatment of at least 4 weeks.

SHOULD RVD CONSOLIDATION THERAPY BE GIVEN FOLLOWING ASCT?

Administration of RVD consolidation following ASCT remains controversial. However, all of the published studies utilised two cycles of consolidation RVD following ASCT.[2,7,8] An improvement in the rate of ≥VGPR with consolidation was not seen in GEM 2012[7] (although there was an increase in number of patients achieving a complete response [CR]) but was seen across the other studies.[2,6] In the largest of these, the IFM 2009 study, the ≥VGPR increased from 70%

post-ASCT to 78% post-consolidation. The limited benefit of consolidation in the GEM 2012 study may reflect the more intense induction regimen used in this trial.

In the STaMINA study, there was no benefit with regards to PFS or OS with the use of four cycles of consolidation RVD post-ASCT, except for an observed trend for PFS benefit in the high-risk population.[44] In all, 55% of these patients received RVD induction. The median number of induction cycles was not reported, although the median time to recruitment after initiation of therapy was 5.2 months; however, patients could be recruited as long as 12 months after initiation of induction therapy, which might in part explain the blunting of the consolidation effect. In contrast, RVD consolidation prolonged PFS in EMN02 compared to no consolidation; importantly, most patients in this study received a less intensive and different induction therapy with bortezomib/cyclophosphamide/dexamethasone (VCD).[45,46]

In practice, we administer consolidation to patients who have tolerated induction and ASCT without significant toxicity. A second ASCT in patients with high-risk cytogenetics remains a consideration but is beyond the scope of this review. All patients should receive maintenance lenalidomide following ASCT whether or not they receive consolidation therapy.[47]

WHICH TRANSPLANT-INELIGIBLE PATIENTS SHOULD I OFFER TRIPLET INDUCTION THERAPY?

Multiple myeloma is a disease of the older patient and decisions regarding therapy must take into account comorbidities and expected lifespan. As demonstrated by Palumbo et al.,[48] frailty as assessed by the International Myeloma Working Group (IMWG) frailty score (age, Katz Activity of Daily Living, Lawton Instrumental Activity of Daily Living, Charlson Comorbidity index) predicts adverse events on therapy, treatment discontinuation and OS. Of note, 19.2% of frail patients across the three clinical studies utilised to assess the score, discontinued therapy at 4 months and 31.2% at 12 months.

Other frailty scores have been reported, including a simplified score published by the Mayo group incorporating age, performance status and N-terminal pro B-type natriuretic peptide (NT-proBNP).[49] This score similarly stratifies patients well on the basis of OS and is simpler to calculate in an outpatient clinic setting. There is no available evidence regarding using these frailty scores to dictate choice of therapy.

In practice, we calculate a frailty score on all newly diagnosed patients with MM. We take this score into account when making a decision regarding selection of therapy; however, would still consider the use of RVD, in a dose-attenuated schedule (Table 3), even in the frail group of patients, particularly those defined as frail based on age alone. Studies that evaluate commencement of doublet therapy to minimise toxicity and

escalation (dose or addition of another agent) in the setting of poor response would be of utility in this patient group.

Many healthcare systems do not currently have access to mAb therapy in the front-line setting. In those jurisdictions with access, DRd and D-VMP are alternative triplets that may be utilised in the transplant-ineligible population. Patient comorbidities may assist in driving this decision, e.g., in a patient with pre-existing peripheral neuropathy or who for peripheral neuropathy would be significant disabling, a non-bortezomib containing triplet may be preferred. In patients with high-risk disease, we prefer to utilise a regimen that incorporates a proteasome inhibitor and consider addition of a mAb.

WHAT STRATEGIES CAN I EMPLOY TO MINIMISE TOXICITIES AND OPTIMISE CONTINUATION OF THERAPY IN A TRANSPLANT-INELIGIBLE PATIENT?

Due to higher rates of toxicity and drug discontinuation in older patients,[48] we utilise attenuated RVD regimens in transplant-ineligible patients deemed suitable for triplet therapy. The SWOG S0777 study (Table 4) provided the pivotal data to support this treatment approach; however, we preferably use weekly bortezomib in this patient cohort given the lower rates of peripheral neuropathy in other regimens[36] and in published studies utilising RVD.[3,15] In addition, we use subcutaneous administration due to the lower incidence of peripheral neuropathy.[35]

A dose attenuated protocol, RVD Lite, (Table 3), demonstrated response rates and PFS comparable to the SWOG S0777 study utilising a 35-day cycle, weekly bortezomib and dose attenuated lenalidomide.[3] This study utilised nine induction cycles followed by six consolidation cycles and maintenance lenalidomide was at the discretion of the physician. This prolonged requirement for visits for parenteral therapy may not be suitable for all older patients. Of note, even with dose attenuation, dose modifications occurred in 39 (78%) patients: 19 (38%) for bortezomib, 27 (54%) for lenalidomide and 32 (64%) for dexamethasone.

RVD Lite and other dose-attenuated regimens (RVD Premium Lite, RVD Ultra Lite; Table 3) have been further evaluated in a retrospective single-centre study.[50] Regimen choice was dictated by physician preference. In terms of toxicities, peripheral neuropathy was marginally higher at 8.43% and 8.7% using the RVD Premium Lite and RVD Classic regimens, compared to 7.1% and 7.7% using RVD Lite and RVD Ultra Lite. Therapy change as a result of intolerance was highest utilising RVD Lite (23.8%), followed by RVD Classic (16.7%) and RVD Ultra Lite (10.3%). There was no difference in terms of PFS between the groups.

Depending on patient age, comorbidities and functional status, we either utilise an RVD Premium Lite, RVD Lite, or RVD Ultra Lite protocol (Table 3). In fitter patients, lenalidomide can be administered at 25 mg and dose reduced in the event of toxicity. In frail or older patients, we commence lenalidomide at

TABLE 4 Bortezomib, lenalidomide, dexamethasone (RVD) Phase II and III transplant ineligible/no immediate intent for transplant studies

Study	Patients, n	Cycle length, days	Induction cycles, n	Bortezomib	Lenalidomide	Dexamethasone	Ongoing therapy
Durie et al. 2017[1]	243	21	8	IV 1.3 mg/m² Day 1, 4, 8, 11	25 mg Day 1–14	20 mg Day 1, 2, 4, 5, 8, 8, 11, 12	Continuous lenalidomide/dexamethasone
O'Donnell et al. 2019[3]	50	35	9	SC 1.3 mg/m² Day 1, 8, 15, 22	15 mg Day 1–21	20 mg Day 1, 2, 8, 9, 15, 16, 22, 23 (≤75 years) 20 mg Day 1, 8, 15, 22 (>75 years)	Bortezomib/lenalidomide consolidation ×6 Maintenance at discretion of physician

Abbreviations: IV, intravenous; SC, subcutaneous.

15 mg and increase this if tolerated. In patients aged ≥70 years, we utilise weekly dexamethasone therapy to improve tolerability and usually dose reduce to 20 mg and reduce this further depending on tolerance. Most older patients require dose modification during the course of therapy.

WHAT SUPPORTIVE CARE SHOULD BE UTILISED IN PATIENTS RECEIVING LENALIDOMIDE, BORTEZOMIB AND DEXAMETHASONE?

Given the high risk of varicella zoster reactivation with bortezomib therapy,[51] all patients should receive anti-viral prophylaxis during RVD induction with either oral acyclovir (400 mg *bis in die* [BID]) or valacyclovir (500 mg BID, although the dose should be reduced according to creatinine clearance). Antibiotic prophylaxis remains controversial and the requirement or recommendation for this has varied between the Phase II and Phase III studies. The TEAMM study, in which patients predominantly received thalidomide-based induction therapy, demonstrated an improvement in the primary end-point (first febrile episode or death) with the use of prophylactic levofloxacin; however, despite a reduction in early deaths there was no OS benefit at 12 months, in addition there are concerns about antibiotic resistance with routine use of prophylaxis.[52] *Pneumocystis jirovecii* risk is low during induction therapy for NDMM,[52,53] and despite extensive use, prophylactic trimethoprim/sulfamethoxazole was not mandated in all of the Phase II and III studies. Intravenous immunoglobulin (400 mg/kg every 4 weeks) may be considered in patients as secondary prophylaxis for patients with recurrent bacterial infections and documented hypogammaglobulinaemia.[54]

Lenalidomide in combination with dexamethasone is associated with an increased risk of thrombosis, in particular in the newly diagnosed setting.[55,56] This risk is reduced, but not abrogated, by the use of lower doses of dexamethasone in contemporary regimens.[57] In light of this elevated risk, all phase II and III studies evaluating RVD have mandated venous thromboembolism (VTE) prophylaxis with either aspirin or low-molecular-weight heparin (LMWH) with a risk of ~5% across the studies.[2,4,6,7] Low-dose direct oral anticoagulants (DOACs) have been demonstrated to be efficacious at preventing venous thrombosis in other malignancies[58,59] and represent a more palatable option to patients than LMWH. Prospective evaluation of DOACs as prophylaxis in patients with MM receiving RVD therapy is required. Thrombocytopenia is commonly seen in patients receiving RVD and VTE prophylaxis may require dose modification or temporary interruption. Patients with a baseline platelet count $<50 \times 10^9$/l were excluded from the randomised studies evaluating DOAC thromboprophylaxis in high-risk patients with cancer,[58,59] and prophylaxis was withheld if the platelet count decreased to $<25 \times 10^9$/l in CASSINI[59] and $<50 \times 10^9$/l in AVERT.[58] There are no specific guidelines available regarding management of prophylactic anticoagulation in the

setting of treatment-induced thrombocytopenia in myeloma and in practice the decision to withhold prophylactic anti-coagulation depends not only on the severity of thrombocytopenia but also other patient risk factors for bleeding and thrombosis.

In prospective studies, the administration of prophylactic normal saline has been demonstrated to minimise fatigue and neurotoxicity, even with the use subcutaneous administration of bortezomib.[60,61] Mechanisms for this remain to be determined but proposed mechanisms include a perfusion effect on inflammatory mediators produced at time of bortezomib administration affecting the small fibres in the skin and their related microvasculature.

All patients with NDMM should receive nitrogen-containing bisphosphonate therapy as per available guidelines.[62,63] Due to a shorter infusion time and a significant reduction in the mortality rate, zoledronic acid may be preferred over pamidronic acid. Denosumab might be considered over zoledronic acid in patients with renal dysfunction or refractory hypercalcaemia.[64] Intravenous immunoglobulin (400 mg/kg every 4 weeks) may be considered in patients with recurrent bacterial infections and documented hypogammaglobulinaemia.[54]

As a final remark, MM is considered a disease at low risk of developing tumour lysis syndrome (TLS)[65] and considering the cutaneous toxicity of allopurinol, especially in addition to lenalidomide and trimethoprim/sulfamethoxazole, there is no evidence to routinely include TLS prophylaxis.

We administer valaciclovir prophylaxis, 500 mg BID, for all patients receiving RVD given the risk of varicella reactivation with bortezomib.

We do not routinely administer fluoroquinolone prophylaxis to patients receiving RVD therapy because of concerns regarding multi-resistant organisms.

We administer sulfamethoxazole 800 mg/160 mg BID to all patients during the induction phase. We often delay introduction of this to cycle two due to the relatively high rate of sulfa allergy.

We administer intravenous immunoglobulin (400 mg/kg every 4 weeks) in those patients with hypogammaglobulinaemia who have had a serious infectious complication on treatment and consider primary prophylaxis in patients at risk of infection who have severe hypogammaglobulinaemia (<4 g/l excluding paraprotein).

In practice, in patients with no additional risk factors for VTE, we use low-dose aspirin and in those with additional risk factors, we use prophylactic dose LMWH as per the IMWG recommendations.[66] The decision to withhold prophylactic anticoagulation in the setting of thrombocytopenia is individualised depending on the patients risk factors for both thromboembolism and bleeding, but we would always withhold prophylaxis if the platelet count is <30 × 10⁹/l.

We do not routinely administer TLS prophylaxis with allopurinol, unless the patient meets the criteria for a higher risk of lysis.[65] In high-risk patients, fluid hydration, allopurinol 100 mg/m² orally three-times daily and regular monitoring of electrolyte and renal function would be employed.[67]

HOW DO I MANAGE HAEMATOLOGICAL TOXICITIES ON LENALIDOMIDE, BORTEZOMIB, DEXAMETHASONE THERAPY?

Haematological toxicities are common with the use of RVD, with Grade 3 or worse neutropenia was seen in 12.9% of patients in GEM 2012,[7] 21.6% of patients receiving RVD in GRIFFIN[7,8] and 14% in those treated with RVD Lite.[3] Grade ≥3 thrombocytopenia was seen in 6.3%, 8.8% and 2% respectively. Grade ≥3 infection is also common, with rates of 9.2% in GEM 2012, 21.6% in GRIFFIN and was not specifically reported in RVD Lite.

Haematological toxicities can be readily managed with dose modification of lenalidomide and bortezomib and in the situation of isolated neutropenia, G-CSF can be utilised to maintain dose intensity and avoid treatment interruptions.

HOW DO I MANAGE PERIPHERAL NEUROPATHY IN PATIENTS RECEIVING RVD?

Bortezomib induced peripheral neuropathy is typically a small fibre neuropathy presenting with distal, symmetric sensory symptoms including paraesthesia, dysesthesia and pain.[68] Motor involvement is uncommon; however, autonomic dysfunction is seen not infrequently.[68] Grade 3 or 4 neurological adverse events were reported in 33% of patients receiving RVD in SWOG S0777 (with a rate of 11% in the Rd arm), while the rate of Grade ≥3 peripheral neuropathy during induction was reported in 4% of patients in GEM 2012 and 8% in GRIFFIN.[7] The RVD-Lite study reported a numerically lower rate of Grade ≥3 peripheral neuropathy of 2%. Neurotoxicity with bortezomib is generally reversible with cessation or dose reduction.

As shown in a recent report[39] and prior published experience[69,70] neuropathy may be in part prevented or mitigated by the infusion of normal saline at the time of bortezomib administration, as well as other supportive measures including emollients.

If feasible, we consider administration of an infusion of 500 ml of normal saline intravenously on day of bortezomib treatment to prevent development of peripheral neuropathy.

In patients who develop Grade 1 neuropathy with pain or Grade 2 neuropathy, we de-escalate bortezomib therapy. If patients are receiving a twice weekly regimen, we move to a weekly regimen (i.e., move from RVD Classic to RVD Premium Lite, Table 3). If bortezomib is already being administered weekly, we institute a dose reduction to the next dose level (dose levels are 1.3, 1 and 0.7 mg/m²).

In patients who develop Grade 2 neuropathy with pain or Grade 3 neuropathy, we withhold bortezomib therapy until the symptoms resolve. We then re-introduce therapy at the next dose level.

In case of established neuropathy, we either utilise gabapentin (initially 300 mg three-times daily but may be increased to 1200 mg three-times daily) or pregabalin (up to 300 mg BID). In the case of poor response or major side-effects to these agents, alternative options are opioids such as fentanyl, tramadol or buprenorphine, but also inhaled medical cannabis may be considered.[71,72]

HOW DO I MANAGE IMMUNOMODULATORY IMIDE DRUG INDUCED BILE ACID MALABSORPTION AND DIARRHOEA?

In a subset of patients, lenalidomide can cause bile acid malabsorption resulting in diarrhoea.[73,74] This can significantly impact on quality of life and result in premature discontinuation of treatment. Patients should be advised to reduce dietary fat intake to <20% and a bile acid sequestrant (such as colesevelam or cholestyramine) can be initiated.[75] This has been demonstrated in a small cohort of 12 patients to improve symptoms in all patients and result in complete resolution in six.[73] Patients were administered up to 6×625 mg of colsevelam in split doses with food, >4 h before/after lenalidomide (and any other dose critical medications).[73] Colestipol 1 g orally 30 min before meals is used in the United States as a similar approach.

In patients with diarrhoea secondary to lenalidomide therapy, we consider dose reduction if appropriate. If a dose reduction is not considered appropriate or diarrhoea persists despite dose reduction, we advise a reduction in fat intake and commence a bile acid sequestrant ensuring this is taken >4 h before or after lenalidomide and other essential medications.

HOW DO I MANAGE SUSPECTED DRUG-INDUCED RASH ON RVD THERAPY?

Drug-related rash is relatively common with RVD therapy. Skin toxicity was seen in up 20% of patients in clinical trials, being Grade 3–4 in 3%.[2,7] Review of other potential aetiologies must be considered, as co-prescribed prophylactic antimicrobials or allopurinol may be responsible.

If lenalidomide is suspected, then oral antihistamines and corticosteroids can be utilised to manage Grade 1 rash. In practice, we typically withhold lenalidomide for Grade 2 or 3 rash, manage symptomatically with oral antihistamines and oral corticosteroids if necessary and restart with corticosteroid cover.[76,77] In patients with recurrent rash, we observed some success with slow up-titration of dose, starting at 5 mg alternate days. Lenalidomide desensitisation can also be considered.[78–80] Patients with Stevens-Johnson syndrome or toxic epidermal necrolysis require permanent drug cessation.[76]

WHAT ARE THE FUTURE DIRECTIONS AND HOW SHOULD THERAPY BE SEQUENCED?

Given the importance of induction therapy in initial disease control and providing prolonged PFS in first remission, induction regimens considered more potent than RVD have been pursued. Based on efficacy in the relapsed/refractory setting, carfilzomib/lenalidomide/dexamethasone (KRd) was trialled as an induction strategy in NDMM in ENDURANCE.[20] This study demonstrated no difference with regards to PFS between KRd and RVD and considering these results, RVD remains the standard of care (Figure 2). Of note, this study did not incorporate up-front ASCT and excluded certain high-risk patients. The role of KRd-based induction as initial therapy continues to be explored, including a recently published Phase II study in NDMM that evaluated four cycles of KRd induction, ASCT, four cycles of KRd consolidation and 10 cycles of KRd maintenance. This study recruited 76 patients, with high-risk patients accounting for 36% of the cohort, and achieved impressive response rates with the stringent CR rate reaching 76%.[18] A second Phase II study by Roussel et al.[81] evaluating KRd induction, ASCT and KRd consolidation in a transplant-eligible cohort demonstrated similar findings.

Incorporation of daratumumab in induction therapy has improved response rates and improved PFS and OS.[8,21,33] Specifically, the addition of daratumumab in the GRIFFIN study and isatuximab in GMMG-HD7 to RVD improved stringent response rates and MRD negativity.[8,28,29] In addition, although GRIFFIN was not powered to evaluate survival, it has demonstrated a PFS benefit with the addition of daratumumab.[29]

Use of RVD induction with or without ASCT, followed by maintenance lenalidomide therapy, provides patients with 3–5 years of PFS and a variety of effective therapeutic options at relapse. These options include daratumumab in combination with bortezomib-dexamethasone,[82,83] daratumumab or isatuximab in combination with pomalidomide-dexamethasone[84,85] or carfilzomib-dexamethasone[86,87] and pomalidomide, bortezomib and dexamethasone.[88] For healthcare systems with limited access to immunotherapeutic agents, addition of cyclophosphamide to both pomalidomide-dexamethasone and carfilzomib-dexamethasone has been demonstrated to be efficacious.[89,90] Selection of the treatment regimen to use at first relapse will depend on patient and disease characteristics and access to regimens. The emerging role of immunotherapy in the relapsed setting, including antibody–drug conjugates, bispecific antibodies and chimeric antigen receptor T-cell therapy (CAR-T) will also allow clinicians to judiciously expand the therapeutic armamentarium at first relapse.

It is currently reasonable to propose that the ultimate goal in the treatment of MM is the achievement of a functional cure, or at the very least sustained disease control for an increasing proportion of our patients, with preservation of quality of life. Approaches being investigated to
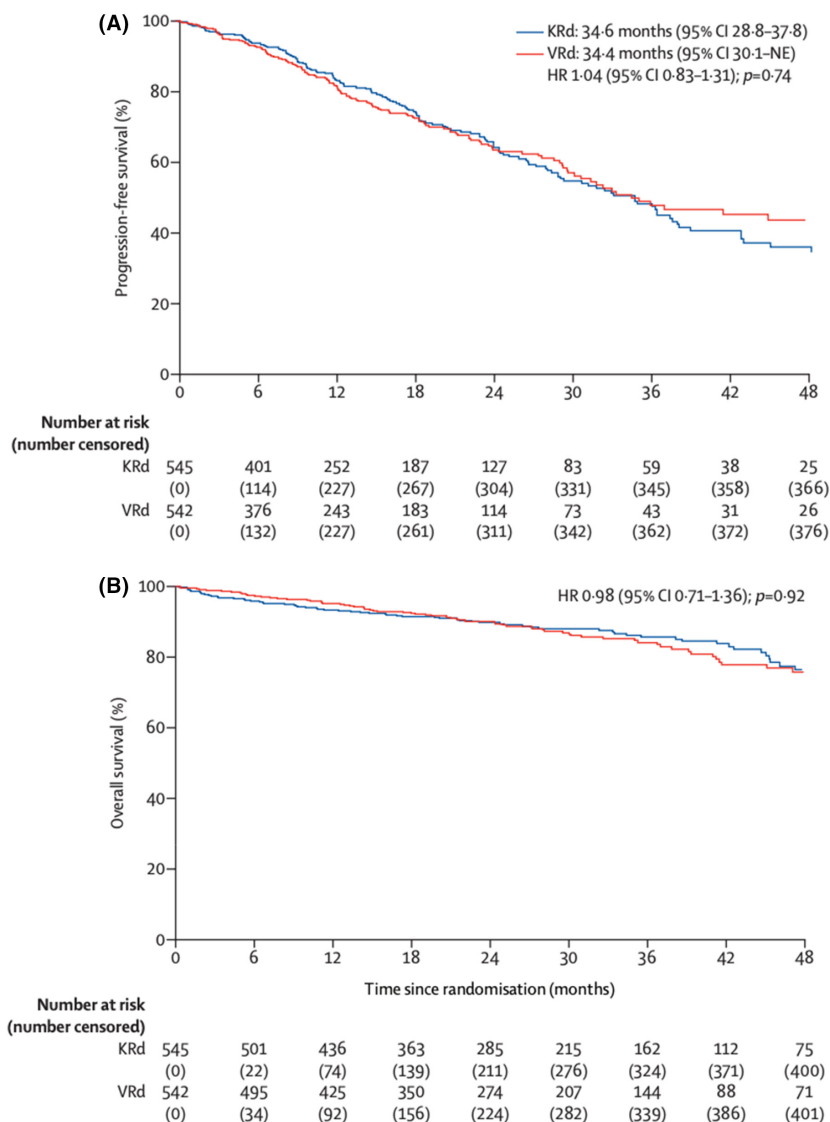
FIGURE 2 Kaplan–Meier estimates of progression-free survival and overall survival comparing KRd and VRd in ENDURANCE study. CI, confidence interval; HR, hazard ratio; KRd, carfilzomib, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

achieve deeper responses and ultimately potentially cure or prolonged and durable remission include the treatment of high-risk asymptomatic or smouldering patients,[91–93] and more intensive treatment approaches guided by response to therapy and achievement of MRD.[94,95] Incorporation of immunotherapeutic agents during initial treatment will be required to achieve this, and RVD represents a highly effective and well tolerated backbone regimen for these approaches, whilst keeping more salvage strategies in reserve and so providing a real-world treatment platform for our patients more broadly.[96] Potential future directions include intensification of therapy with the addition of immunotherapy and cytoreductive treatment targeting 'stemness' from the outset and then potentially de-escalation depending on response or achievement of MRD. Alternatively to debulk initially with combined therapies, and then utilise targeted immunotherapeutic approaches to harness the immune system to target residual disease, is another tailored approach to further improve outcome.[97] Finally, and most importantly in the current era, RVD provides (with the advent of bortezomib and lenalidomide becoming generic), a cost-effective and resource constrained option for patients in diverse healthcare systems, with practical accessibility on a global scale.[98]

AUTHOR CONTRIBUTIONS
Georgia J. McCaughan developed the first draft and edited and wrote the manuscript. Sara Gandolfi, John J. Moore and Paul G. Richardson edited and wrote the manuscript.

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CONFLICT OF INTEREST

Georgia J. McCaughan reports advisory board participation and honoraria from Janssen. Paul G. Richardson reports institutional grant support from Bristol Myers Squibb/Celgene, Karyopharm, Oncopeptides AB, and Takeda; consulting fees for advisory committee service from Bristol Myers Squibb/Celgene, Karyopharm, Oncopeptides AB, GlaxoSmithKline, Janssen, Sanofi, and Takeda. Sara Gandolfi and John J. Moore have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the present study.

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