REVIEW ARTICLE

Clinical perspectives on the optimal use of lenalidomide plus bortezomib and dexamethasone for the treatment of newly diagnosed multiple myeloma

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Abstract

To improve the outcomes of patients with the otherwise incurable hematologic malignancy of multiple myeloma (MM), a key paradigm includes initial treatment to establish disease control rapidly followed by maintenance therapy to ensure durability of response with manageable toxicity. However, patients' prognosis worsens after relapse, and the disease burden and drug toxicities are generally more challenging with subsequent lines of therapy. It is therefore particularly important that patients with newly diagnosed multiple myeloma (NDMM) receive optimal frontline therapy. The combination of lenalidomide, bortezomib, and dexamethasone (RVd) has consistently demonstrated a tolerable safety profile with significant and clinically relevant benefit, including deep and durable responses with improved survival in patients with NDMM regardless of their transplant eligibility. Furthermore, comparative studies evaluating this triplet regimen against both doublet and other triplet regimens have established RVd as a standard of care in this setting based upon its remarkable and concordant efficacy. Given the breadth of clinical data, physician familiarity, inclusion in treatment guidelines, and the emerging potential of RVd-containing quadruplet regimens, RVd will likely continue as a key cornerstone of the treatment of NDMM, and its role will therefore likely continue to grow as a therapeutic backbone in the initial treatment of MM.

Introduction

Combinations of lenalidomide, bortezomib, and dexamethasone (RVd) are recommended for the treatment of newly diagnosed multiple myeloma (NDMM).[1,2] Lenalidomide and bortezomib are approved for use in the USA for either transplant-ineligible (TNE) or transplant-eligible (TE) patients with NDMM. In 2019, RVd was approved in the European Union (EU) for patients with TNE NDMM[3] and is used in Switzerland, Australia, and Brazil for NDMM regardless of transplant eligibility.

In NDMM trials, RVd has achieved deep, durable responses that are among the best reported with triplet regimens, which have been further improved with the introduction of monoclonal antibodies.[4] The efficacy and tolerability of RVd have been demonstrated in TNE and TE populations across numerous studies and dose schedules. This review summarizes data supporting RVd as standard of care in NDMM when administered as induction therapy in settings of autologous stem cell transplant (ASCT) or in TNE patients, and as part of emerging quadruplet regimens.

RVd: rationale and background

MM remains incurable, despite therapeutic advances having led to substantially improved progression-free (PFS) and overall survival (OS).[5,6] Disease burden, toxicities, and outcomes typically worsen with each subsequent line of therapy, confirming critical needs for effective frontline intervention.[7] Achieving sustained deep responses (very good partial response [VGPR], complete response [CR], minimal residual disease [MRD] negativity) is a key treatment goal for NDMM and can improve survival.[8-10] Frontline regimens should be highly effective and tolerable to attain successful induction and maintain continuous therapy. Avoiding agents that deplete stem cells and interfere with their collection is important in order to preserve the option of ASCT.

Lenalidomide (an immunomodulatory agent) and bortezomib (a proteasome inhibitor) are backbones of pharmacotherapy for NDMM.[1,5] Lenalidomide has pleiotropic mechanisms of action and can synergistically enhance antimyeloma effects of other drugs (e.g., dexamethasone).[11-13] The efficacy and tolerability of lenalidomide + dexamethasone (Rd) in NDMM have been demonstrated in multiple trials, including the phase III FIRST study, which established continuous Rd treatment in TNE NDMM.[14,15] Likewise, bortezomib enhances the antimyeloma activity of dexamethasone and other agents[16-18] and has been evaluated extensively in NDMM.[19] Rd has synergistic activity, as confirmed in relapsed/refractory MM (RRMM) phase I/II studies in which lenalidomide-exposed and bortezomib-exposed patients achieved durable responses, with favorable toxicity.[20,21] Each drug individually, especially bortezomib, has positive effects on bone metabolism.[22,23] Since the treatment landscape has shifted toward triplet regimens due to their improved efficacy over doublet regimens, clinical evaluations of RVd in NDMM have accelerated. With the success of RVd in NDMM, newer agents have been evaluated in this setting with Rd, including carfilzomib,[24] ixazomib,[25] daratumumab (DARA),[26] and elotuzumab.[27]

RVd: phase II studies in newly diagnosed multiple myeloma

The RVd regimen was initially evaluated with bortezomib administered intravenously (IV) (Table 1). In the first and seminal phase I/II trial, following RVd induction, patients achieving a partial response (PR) or better could undergo ASCT, and all responding patients could then receive tailored RVd maintenance after eight cycles.[28] The randomized phase II EVOLUTION trial, which included lenalidomide and bortezomib with weekly dexamethasone treatment (the so-called VRd regimen) *versus* three other bortezomib-, dexamethasone-, and cyclophosphamide-containing regimens, in patients with TE or TNE NDMM followed.[29] This study demonstrated a combined efficacy and manageable toxicity profile (including the lowest rates of grade ≥3 hematologic and overall adverse events [AE] among the evaluated regimens), which warranted further investigation in phase III trials.[29] The IFM 2008 trial evaluated RVd, administered in three 21-day cycles, in TE patients with NDMM.[30] Patients then proceeded to ASCT, after which those who had not progressed received two 21-day cycles of RVd consolidation. This study demonstrated the favorable efficacy of the RVd regimen in TE patients.

The second wave of phase II RVd trials (using subcutaneous [SC] bortezomib) provided supporting data, exploring different dosing strategies, such as the RVd Lite regimen designed to minimize toxicities in older TNE patients by using lower dose intensities.[31-33] Notably, promising results from the phase II GRIFFIN trial evaluating quadruplet RVd-DARA *versus* RVd[34,35] have led to implementation of RVd as a basis for quadruplet regimens, which are poised for inclusion in the NDMM treatment paradigm.[34,36] Key characteristics of the study populations, outcomes, and selected safety findings of these phase II studies are shown in Table 1, and the phase II RVd dosing schedules are shown in Table 2.

RVd: phase III studies in newly diagnosed multiple myeloma

Phase III studies have further supported the use of RVd in NDMM (Table 3). The pivotal SWOG S0777 trial demonstrated greater efficacy of RVd than Rd in patients not intended for immediate ASCT, supporting regulatory approval of RVd.[3,37] Patients randomly assigned to RVd received eight 21-day cycles (Table 2), followed by Rd maintenance. After a median follow-up of 7 years, improved PFS (median, 41 *vs*. 29 months; *P*=0.003) (Figure 1A) and OS (median, not reached [NR] *vs*. 69 months; *P*=0.0114) (Figure 1B) were observed with RVd *versus* Rd.[38] RVd also improved depth of response, with 75% of patients achieving ≥VGPR *versus* 53% with Rd. Rates of toxicities were generally similar between the treatment groups, but more grade ≥3 neurologic toxicities were observed with RVd than with Rd (34.6% *vs*. 11.3%, respectively), likely due to the use of IV bortezomib. A *post-hoc* analysis of this trial also evaluated RVd *versus* Rd in patients stratified by age.[39] In patients <65 years of age (n=269), improved PFS (median, 55.4 *vs.* 36.6 months; hazard ratio [HR]=0.63, 95% confidence interval [95% CI]: 0.46-0.87) and OS (median, NR *vs.* 68.9 months; HR=0.61, 95% CI: 0.39-0.97) were observed with RVd *versus* Rd. Higher rates of grade ≥3 treatment-emergent adverse events (TEAE) (87 *vs*.

Table 1. Phase II studies evaluating RVd in patients with newly diagnosed multiple myeloma.[a]

Study	Population	Response	PFS and OS	Selected safety findings
Richardson *et al.*[28] (NCT00378105) Regimen: 8 × 21-day cycles of RVd (optional ASCT after 4 cycles if ≥PR) → RVd maintenance after 8 cycles (if responding)[b]	N=66 Phase II: N=35	Phase II (best response): ORR: 100% ≥VGPR: 74% All patients (best response): ORR: 100% ≥VGPR: 67%	18-mth PFS rate: 75% 18-mth OS rate: 97%	Grade 3/4 AE Lymphopenia: 14% Neutrophils: 9% Platelets: 6% Neuropathic pain: 3% Neuropathy, sensory: 2% Neuropathy, motor: 2% No grade 4 neuropathy
EVOLUTION[29] (NCT00507442) Regimens: (8 × 21-day cycles of RVd *vs.* VDC *vs.* VDC-mod *vs.* VDCR) → BORT maintenance	N=140 RVd: N=42 (98% TE)	ORR (best response): 85% ≥VGPR (best response): 51%	1-yr PFS rate: 83% 1-yr OS rate: 100%	Grade ≥3 AE Neutropenia: 10% Thrombocytopenia: 12% Neuropathy: 17%
IFM 2008[30] (NCT01206205) 3 × 21-day cycles of RVd → ASCT → 2 cycles of RVd consolidation → LEN maintenance (+ BORT if patient had high-risk features)	N=31 TE patients	ORR (end of consolidation): 97% ≥VGPR (end of consolidation): 87% ORR (best response at any time): 100% ≥VGPR (best response at any time): 84%	3-yr PFS rate: 77% 3-yr OS rate: 100%	Grade 3/4 AE (during RVd induction or consolidation) Neutropenia: 35% Thrombocytopenia: 13% Grade 3/4 AE (reported at any time) Neutropenia: 65% Thrombocytopenia: 19% No grade 3/4 neuropathy
CTRIAL-IE (ICORG) 13-17[33] (NCT02219178) 4 × 21-day cycles of RVd → (ASCT or 4 more cycles of RVd) → LEN maintenance	N=42 TE or TNE patients	ORR (after 4 cycles of RVd): 92.5%[c] ≥VGPR (after 4 cycles of induction): 62.5%[c]	Not reported	Grade ≥3 related AE Thrombocytopenia: 16.7% Fatigue: 11.9% Neutropenia: 9.5% PN: 4.8% No grade 4 PN
RVd Lite[31] (NCT01782963) 9 × 35-day cycles of RVd Lite → 6 × 28-day cycles of LEN + BORT consolidation → LEN maintenance	N=50 TNE patients	ORR (after 4 cycles of RVd Lite): 86% ≥VGPR (after 4 cycles of RVd Lite): 66%	Median PFS: 35.1 mths Median OS: NR	Grade ≥3 TEAE Hypophosphatemia: 34% Fatigue: 16% Neutropenia: 14% PN: 2% Thrombocytopenia: 2%
FMG-MM02[32] (NCT01790737) 3 × 21-day cycles of RVd → (CY + FIL mobilization *vs.* FIL mobilization) → ASCT → LEN maintenance	N=80 TE patients	ORR (best response at any time): 89% ≥VGPR (best response at any time): 68%	1-/2-/3-yr PFS rates: 78%/67%/52% 1-/2-/3-yr OS rates: 96%/90%/83%	Grade ≥3 AE in patients who received RVd induction (N=78) Neutropenia: 24% Infections: 23%[d] Febrile neutropenia: 22% Thrombocytopenia: 14% PN: 3%

Continued on following page.

Study	Population	Response	PFS and OS	Selected safety findings
GRIFFIN[34, 35] (NCT02874742) (4 × 21-day cycles of RVd *vs.* RVd-DARA) → ASCT → (2 cycles of RVd *vs.* RVd-DARA consolidation) → (LEN *vs.* LEN + DARA maintenance)	N=207 RVd: N=104 RVd-DARA: N=103 TE patients	ORR (by end of induction) RVd: 91.8% RVd-DARA: 98.0% (by end of consolidation) RVd: 91.8% RVd-DARA: 99.0% sCR (by end of induction) RVd: 7.2% RVd-DARA: 12.1% (by end of consolidation) RVd: 32.0% RVd-DARA: 42.4% *P*=.068[e]	1-yr PFS rate RVd: 95.3% RVd-DARA: 96.9% 2-yr PFS rate RVd: 89.8% RVd-DARA: 95.8% 1-yr OS rate RVd: 97.9% RVd-DARA: 99.0% 2-yr OS rate RVd: 93.4% RVd-DARA: 95.8%	Grade 3/4 TEAE Neutropenia RVd: 22% RVd-DARA: 41% Lymphopenia RVd: 22% RVd-DARA: 23% Thrombocytopenia RVd: 9% RVd-DARA: 16% PN[f] RVd: 8% RVd-DARA: 7%
PLEIADES[69] (NCT03412565) RVd-DARA: 4 × 21-day cycles of RVd-DARA VMP-DARA: 9 × 42-day cycles → 28-day cycles until PD Rd-DARA: 28-day cycles until PD	N=199 RVd-DARA: N=67 VMP-DARA: N=67 Rd-DARA: N=65	≥VGPR rate (at primary analysis) RVd-DARA: 71.6% ORR (at primary analysis) VMP-DARA: 88.1% Rd-DARA: 90.8%	Not reported	Grade 3/4 TEAE Neutropenia RVd-DARA: 28.4% VMP-DARA: 37.3% Rd-DARA: 49.2% Lymphopenia RVd-DARA: 16.4% VMP-DARA: 22.4% Rd-DARA: 10.8% Thrombocytopenia RVd-DARA: 14.9% VMP-DARA: 43.4% Rd-DARA: 13.8%

[a]Due to differences in study design and procedures, cross-trial comparisons must be interpreted with caution. [b]RVd maintenance therapy comprised 21-day cycles of lenalidomide (dose tolerated at the end of cycle 8) on days 1-14, bortezomib (dose tolerated at the end of cycle 8) on days 1, 8, and dexamethasone 10 mg on days 1, 2, 8, 9. [c]Of 40 response-evaluable patients. [d]Not including febrile neutropenia. [e]Pre-set one-sided α of 0.1. [f]Grouped term that includes peripheral neuropathy and peripheral sensory neuropathy. AE: adverse events; ASCT: autologous stem cell transplant; BORT: bortezomib; CY: cyclophosphamide; DARA: daratumumab; DEX: dexamethasone; FIL: filgrastim; IV: intravenously; LEN: lenalidomide; NR: not reached; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PN: peripheral neuropathy; PR: partial response; Rd-DARA: lenalidomide, dexamethasone, and daratumumab; RVd: lenalidomide, bortezomib, and dexamethasone; RVd-DARA: lenalidomide, bortezomib, dexamethasone, and daratumumab; RVd Lite: modified lenalidomide, bortezomib, and dexamethasone; sCR: stringent complete response; TE: transplant eligible; TNE: transplant ineligible; TEAE: treatment-emergent adverse events; VDC: bortezomib, dexamethasone, and cyclophosphamide; VDC-mod: bortezomib, dexamethasone, and cyclophosphamide with an additional cyclophosphamide dose; VDCR: bortezomib, dexamethasone, cyclophosphamide, and lenalidomide; VGPR: very good partial response; VMP-DARA: bortezomib, melphalan, prednisone, and daratumumab; mth/mths: month/months; yr: year.

79%) and treatment discontinuation due to toxicity (29 *vs.* 18%) were observed with RVd than with Rd. In patients ≥65 years of age (n=202), PFS (median, 33.1 *vs.* 25.8 months; HR=0.83, 95% CI: 0.60-1.16) and OS (62.9 *vs.* 53 months; HR=0.83, 95% CI: 0.55-1.23) were no longer statistically significant for RVd *versus* Rd. While rates of grade ≥3 TEAE were similar (93% for RVd *vs.* 89% for Rd), discontinuation due to toxicity was higher for RVd (47 *vs.* 26%).

Interim results from the randomized phase III ENDURANCE (E1A11) trial, evaluating RVd *versus* carfilzomib, lenalidomide, and dexamethasone (KRd) in NDMM (regardless of intent to undergo ASCT) demonstrated similar efficacy.[40] In this trial, which enrolled standard-risk patients as well as those with fluorescence *in situ* hybridization (FISH)-identified t(4;14) but excluded those with other high-risk cytogenetics, such as 17p deletion, PFS (censoring at SCT or alternative therapy) was 34.4 *versus* 34.6 months with RVd *versus* KRd, respectively (*P*=0.74), after a median follow-up of 15 months. The rate of ≥CR (14.8% *vs.* 18.3%; *P*=0.13) was also similar, although more patients achieved ≥VGPR with KRd (64.7% vs. 73.8%; *P*=0.0015). Notably, rates of grade ≥3 serious AE overall and cardiac, pulmonary, and

renal AE were lower with RVd than with KRd, while rates of grade 3/4 peripheral neuropathy (PN) were higher.

The DSMM XIV study, evaluating induction with RVd (given as three 21-day cycles) compared with lenalidomide, doxorubicin, and dexamethasone (RAD), followed by response-adapted SCT (autologous or allogeneic) and lenalidomide maintenance, was designed to confirm the noninferiority of RAD for the induction phase primary endpoint of CR rate.[41] In the RVd *versus* RAD arms, the rates of ≥CR were similar (13.0% *vs*. 11.8%), but there were nonsignificant trends toward higher rates of ≥VGPR (46.3% *vs*. 38.9%) and MRD negativity, as determined by next-generation sequencing (26.8% *vs*. 21.3%), with RVd. Rates of grade ≥3 neutropenia and thrombocytopenia were similar in the two arms, whereas grade ≥3 polyneuropathy/neuralgia was observed in 2.1% of patients treated with RVd and none treated with RAD. In an updated analysis (median follow-up, 40.2 months), median PFS from first randomization was longer with RVd than with RAD (53.7 *vs*. 41.7 months; *P*=0.0439).[42]

In the IFM 2009 study, TE patients received three 21-day cycles of RVd induction (Table 2) followed by ASCT and two cycles of RVd consolidation (RVd + ASCT) or three cycles of RVd induction followed by five cycles of RVd consolidation (RVd); lenalidomide maintenance was then administered for 1 year.[43,44] PFS was improved with RVd + ASCT *versus* RVd by approximately 12 months (median, 47.3 *vs*. 35.0 months; HR=0.70; 95% CI: 0.59-0.83; *P*<0.001).[44] Remarkably, OS was similar (HR=1.03; 95% CI: 0.80-1.32; *P*=0.81); the median OS was NR in either arm.[44] The rate of ≥VGPR was higher with RVd + ASCT than with RVd (88% *vs*. 77%; *P*=0.001).[43] Grade 3/4 neutropenia, thrombocytopenia, and febrile neutropenia were more common with RVd + ASCT than with RVd; however, rates of grade 3/4 PN were similar. With a median follow-up of ≥43 months, the incidence of second primary malignancy per 100 patient-years did not differ significantly between patients treated with RVd + ASCT or RVd (1.5 *vs*. 1.1), nor

Table 2. RVd nomenclature and dosing schedules.

Nomenclature[a]	RVd NDMM trials	Population	Cycle length	Lenalidomide	Bortezomib[b]	Dexamethasone
RVd Classic	Richardson *et al.*[28, c] CTRIAL-IE (ICORG) 13-17[33] FMG-MM02[32] SWOG S0777[37] DSMM XIV[41] IFM 2009[43, d] ENDURANCE[40, e] RVD 1000[65] DETERMINATION[45, f]	TE or TE/TNE	21 days	25 mg days 1-14	1.3 mg/m^2 days 1, 4, 8, 11	20 mg days 1, 2, 4, 5, 8, 9, 11, 12
Non-traditional RVd[g]	EVOLUTION[29] IFM 2008[30]	TE or TE/TNE	21 days	25 mg days 1-14	1.3 mg/m^2 days 1, 4, 8, 11	40 mg days 1, 8, 15
Non-traditional RVd[g]	GRIFFIN[34]	TE	21 days	25 mg days 1-14	1.3 mg/m^2 days 1, 4, 8, 11	20 mg days 1, 2, 8, 9, 15, 16
GEM-RVd[g]	GEM 2012[49]	TE	28 days	25 mg days 1-21	1.3 mg/m^2 days 1, 4, 8, 11	40 mg days 1-4, 9-12
RVd Lite	RVd LITE[31]	TNE	35 days	15 mg days 1-21	1.3 mg/m^2 days 1, 8, 15, 22	20 mg ≤75 yr: days 1, 2, 8, 9, 15, 16, 22, 23 >75 yr: days 1, 8, 15, 22
RVd Ultra Lite	-[h]	TNE, frail	28-35 days	15 mg days 1-21	1.3 mg/m^2 days 1, 8, 15	20 mg days 1, 2, 8, 9, 15, 16
RVd Premium Lite	-[h]	TNE	28 days	25 mg days 1-21	1.3-1.6 mg/m^2 days 1, 8, 15, 22	20 mg days 1, 2, 8, 9, 15, 16, 22, 23

[a]RVd regimen nomenclature is not yet standardized. [b]CTRIAL-IE (ICORG) 13-17, RVd LITE, FMG-MM02, DSMM XIV, GRIFFIN, and GEM2012 used SC bortezomib. ENDURANCE used SC or IV bortezomib. All other listed trials used IV bortezomib. SC bortezomib is generally used for the RVd Ultra Lite and RVd Premium Lite regimens, but IV bortezomib may be administered with IV normal saline for those patients who are not tolerant of SC bortezomib. [c]Phase II dosing for this trial. [d]During the consolidation phase of IFM 2009, RVd was administered with dexamethasone 10 mg in the transplant arm. [e]Bortezomib on days 1 and 8 in cycles 9-12; dexamethasone reduced to 10 mg starting in cycle 5, and limited to days 1, 2, 8, and 9 during cycles 9-12. [f]IV or SC bortezomib; dexamethasone dose was 20 mg for cycles 1-3 and reduced to 10 mg starting in cycle 4. [g]The RVd regimens used in these trials do not yet have widely accepted or proposed nomenclatures. [h]Regimen used in some clinics but not yet used in a published phase II or phase II clinical trial. IV: intravenous; NDMM: newly diagnosed multiple myeloma; RVd: lenalidomide, bortezomib, and dexamethasone; SC: subcutaneous; TE: transplant eligible; TNE: transplant ineligible; yr: year.

did the frequency of acute myeloid leukemia (4 cases *vs.* 1 case) or myelodysplastic syndromes (1 case each), although follow-up remained short.[43]

The safety and efficacy of adding ASCT to RVd were also evaluated in the recently reported DETERMINATION study.[45] Eligible patients received one cycle of RVd (Table 2) and were then randomly assigned 1:1 to receive two cycles of RVd with stem cell mobilization followed by either five cycles of RVd (RVd alone) or high-dose melphalan with ASCT and two subsequent cycles of RVd (RVd + ASCT). Both groups received maintenance therapy with daily lenalidomide until disease progression, unacceptable toxicity, or both. With a median follow-up of 76.0 months, PFS was significantly improved with RVd + ASCT *versus* RVd alone (median PFS, 67.5 *vs*. 46.2 months; HR=0.65; 95% CI: 0.52-0.81; *P*<0.001) (Figure 2A). However, no OS benefit with RVd + ASCT over RVd alone was observed (Figure 2B). The 5-year OS in patients with high-risk cytogenetics was greater with RVd + ASCT than with RVd alone (63.4% *vs*. 54.3%). Response rates were similar with RVd + ASCT and RVd alone (≥PR, 97.5% *vs*. 95.0%; ≥VGPR, 82.7% *vs*. 79.6%; ≥CR, 46.8% *vs*. 42.0%). A greater percentage of patients achieved MRD negativity with RVd + ASCT than with RVd alone (54% *vs*. 40%; odds ratio=0.55; 95% CI: 0.30-1.01). In patients who were MRD positive, the median PFS was greater with RVd + ASCT than with RVd alone (50.6 *vs*. 33.4 months), but no difference in median PFS was seen in between the two arms for patients who were MRD negative.

The absence of OS benefit is notable, especially given the use of ASCT in only 28% of patients in the delayed transplant arm to date.[46] This is in contrast to the IFM/DFCI 2009 study in which salvage ASCT was used in almost 80% of patients.[44] Moreover, while the overall rate of second primary malignancies was similar in both arms, ten cases of acute myeloid leukemia or myelodysplastic syndromes were seen in the transplant arm compared to no cases in the RVd-alone arm by the time of data cutoff (October 2021; *P*=0.002).[47] Considering that four of the ten patients who developed acute myeloid leukemia or myelodysplastic syndromes had died by the time of data cutoff, careful monitoring is warranted. Finally, during ASCT, a significant and clinically meaningful decrease in quality of life occurred, which proved transient after several

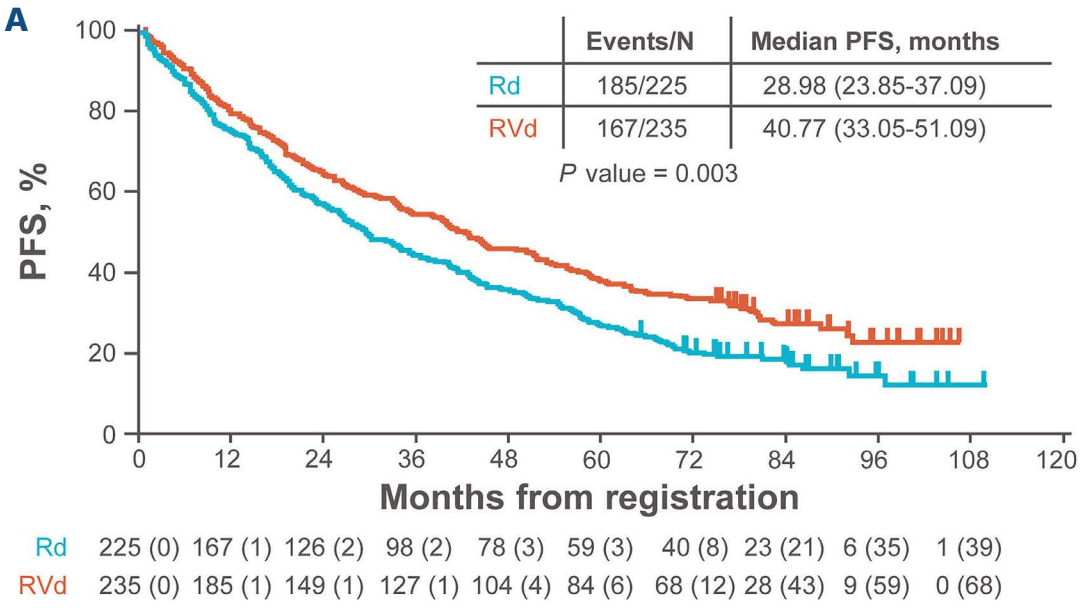

Figure 1. Progression-free survival and overall survival for RVd *vs* Rd in the SWOG S0777 trial (median follow-up, 84 months) (A) Progression-free survival. (B) Overall survival. Figures reprinted from Durie BGM, *et al*. Blood Cancer J. 2020;10(5):53. Creative Commons Attribution 4.0 International License (*https://creativecommons.org/licenses/by/4.0/*).[38] NR: not reached; OS: overall survival; PFS: progression-free survival; Rd: lenalidomide + dexamethasone; RVd: lenalidomide, bortezomib, and dexamethasone.

Table 3. Phase III studies evaluating RVd in patients with newly diagnosed multiple myeloma.[a]

Study	Population	Response	PFS and OS	Selected safety findings
SWOG S0777[37,38] (NCT00644228) 8 × 21-day cycles of RVd *vs.* 6 × 28-day cycles of Rd → Rd maintenance[b]	N=525 RVd: N=264 (N=215 for ORR; N=235 for PFS and OS) Rd: N=261 (N=207 for ORR; N=225 for PFS and OS) Patients not planned for immediate ASCT	ORR RVd: 90.2% Rd: 78.8% ≥VGPR RVd: 74.9% Rd: 53.2% CR RVd: 24.2% Rd: 12.1%	Median PFS RVd: 41 mths Rd: 29 mths *P*=0.003 Median OS RVd: NR Rd: 69 mths *P*=0.0114	Grade ≥3 AE[c] Blood or bone marrow RVd: 47.3% Rd: 46.0% Infection[d] RVd: 14.5% Rd: 13.7% Neurological[e] RVd: 33.2% Rd: 11.1% Pain[e] RVd: 12.0% Rd: 4.0%
DSMM XIV[41,42] (NCT01685814) 3 × 21-day cycles of RVd *vs.* 3 × 28-day cycles of RAD → response-adapted SCT and LEN maintenance	476 patients randomized 469 received ≥1 dose of study drug RVd: N=237 RAD: N=232 TE patients	≥CR (post-induction) RVd: 13.0% RAD: 11.8% *P*=0.697 ≥VGPR (post-induction) RVd: 46.3% RAD: 38.9% *P*=0.110	Median PFS (from first randomization) RVd: 53.7 mths RAD: 41.7 mths *P*=0.0439	Grade ≥3 TEAE Neutropenia RVd: 5.5% RAD: 6.5% Thrombocytopenia RVd: 2.1% RAD: 2.6% PN/neuralgia RVd: 2.1% RAD: 0%
IFM 2009[43] (NCT01191060) 3 × 21-day cycles of RVd → 5 × 21-day cycles of RVd alone[f] *vs.* ASCT + 2 × 21-day cycles of RVd[f] → LEN maintenance	N=700 RVd alone: N=350 RVd + ASCT: N=350 TE patients	ORR (best response) RVd alone: 97% RVd + ASCT: 98% *P*=0.02[g] ≥VGPR (best response) RVd alone: 77% RVd + ASCT: 88% *P*=0.001 CR (best response) RVd alone: 48% RVd + ASCT: 59% *P*=0.03	Median PFS RVd alone: 36 mths RVd + ASCT: 50 mths *P*<0.001	Grade 3/4 AE Neutropenia RVd alone: 47.4% RVd + ASCT: 92.0% Febrile neutropenia RVd alone: 3.4% RVd + ASCT: 14.9% Thrombocytopenia RVd alone: 14.3% RVd + ASCT: 83.1% Anemia RVd alone: 8.9% RVd + ASCT: 19.7% PN RVd alone: 12.0% RVd + ASCT: 12.9%
DETERMINATION[45] (NCT01208662) 3 × 21-day cycles of RVd → stem cell collection → 5 × 21-day cycles of RVd alone *vs.* high-dose MEL + ASCT + 2 × 21-day cycles of RVd → LEN maintenance until PD	N=873 RVd + ASCT: N=365 RVd alone: N=357	ORR (best response) RVd + ASCT: 97.5% RVd alone: 95.0% ≥VGPR (best response) RVd + ASCT: 82.7% RVd alone: 79.6% CR (best response) RVd + ASCT: 46.8% RVd alone: 42.0%	Median PFS RVd + ASCT: 67.5 mths RVd alone: 46.2 mths *P*<0.0014	Grade ≥3 TEAE Neutropenia RVd + ASCT: 86.3% RVd alone: 42.6% Thrombocytopenia RVd + ASCT: 82.7% RVd alone: 19.9% Leukopenia RVd + ASCT: 39.7% RVd alone: 19.6%

Continued on following page.

Study	Population	Response	PFS and OS	Selected safety findings
PETHEMA/ GEM2012[49] (NCT01916252) 6 × 28-day cycles of RVd → ASCT (IV busulfan + MEL) *vs.* ASCT (MEL) → 2 × 28-day cycles → RVd consolidation	N=458 TE patients	ORR (after induction): 83.4% ≥VGPR (after induction): 66.6% ORR (after ASCT): 81.2% ≥VGPR (after ASCT): 75.1% ORR (after consolidation): 80.6% ≥VGPR (after consolidation): 75.5%	Median PFS: NR	Grade 3/4 AE through induction Neutropenia: 12.9% Thrombocytopenia: 6.3% Infection: 9.2% PN: 3.9%[h]
ENDURANCE (E1A11)[40] (NCT01863550) 12 × 21-day cycles of RVd *vs.* 9 × 28-day cycles of KRd → LEN maintenance × 2 years *vs.* LEN maintenance until PD	N=1087 RVd: N=542 (N=527 for ORR, safety) KRd: N=545 (N=526 for ORR, safety) Patients not planned for early ASCT	ORR (after induction) RVd: 84.3% KRd: 86.7% *P*=0.13 ≥VGPR (after induction) RVd: 64.7% KRd: 73.8% *P*=0.0015 ≥CR (after induction) RVd: 14.8% KRd: 18.3% *P*=0.26	Median PFS RVd: 34.4 mths KRd: 34.6 mths *P*=0.74 3-yr OS RVd: 84% KRd: 86%	Grade ≥3 cardiac, pulmonary, and renal RVd: 4.7% KRd: 16.0% *P*<0.0001 Grade 3/4 PN RVd: 8.3% KRd: 0.8% Grade 3-5 SAE RVd: 22.0% KRd: 44.5% *P*<0.0001

[a]Due to differences in study design and procedures, cross-trial comparisons must be interpreted with caution. [b]Stem cell collection was allowed for patients considering future transplant. [c]AE considered to be unlikely related to treatment were stated to be excluded from reporting in the SWOG S0777 publication. [d]Reported as a hematologic AE. [e]Reported as a neurological AE. [f]During consolidation, patients received a reduced daily dose of DEX 10 mg. [g]*P* value for "best response during the study" overall. [h]PN was a grouped term including PN, neuralgia, polyneuropathy, and sensory loss. AE: adverse events; ASCT: autologous stem cell transplant; CR: complete response; DEX: dexamethasone; IV: intravenously; KRd: carfilzomib, lenalidomide, and dexamethasone; LEN: lenalidomide; MEL: melphalan; NR: not reached; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PN: peripheral neuropathy; RAD: lenalidomide, doxorubicin, and dexamethasone; Rd: lenalidomide + dexamethasone; RVd: lenalidomide, bortezomib, and dexamethasone; SAE: serious adverse events; SCT: stem cell transplant; TE: transplant eligible; TEAE: treatment-emergent adverse events; VGPR: very good partial response; VMP; bortezomib, melphalan, and prednisone; mths: months.

months and then improved over time.[45] These findings corroborate similar results seen in the IFM/DFCI 2009 trial.[48]

In the PETHEMA/GEM2012 study, patients with TE NDMM received six 28-day cycles of RVd induction (Table 2) followed by ASCT with IV busulfan + melphalan *versus* melphalan and RVd consolidation (2 cycles).[49] The RVd schedule was devised to increase lenalidomide and dexamethasone dose intensity in order to maximize response. At a median follow-up of 84.4 months, the median PFS was 80.8 months.[50] An induction analysis of the pooled population showed that the rate of ≥VGPR was 66.6% and increased with more cycles during RVd induction, ranging from 55.6% to 70.4% for cycles 3-5 and post-induction, respectively. The rate of MRD negativity after induction was 28.8%. Common grade 3/4 AE were neutropenia, infection, and thrombocytopenia. The rate of grade 3/4 PN (including neuralgia, polyneuropathy, and sensory loss) was 3.9%.

The bortezomib, thalidomide, and dexamethasone (VTD) regimen has been used in NDMM outside of the USA,[51] with no randomized controlled trials comparing RVd *versus* VTD conducted to date. Thus, findings from the PETHEMA/GEM2005, PETHEMA/GEM2012, IFM 2009, and IFM 2013-04 trials were used to conduct an integrated analysis[52] evaluating RVd *versus* VTD in TE NDMM.[43,49,53,54] In the GEM studies, the rate of ≥VGPR after induction was higher with RVd than with VTD (70.1% *vs*. 55.9% at cycle 6); findings from the IFM analyses (four 21-day–cycle regimens) showed noninferiority between RVd (57.1%) and VTD (56.5%). Safety findings were consistent with the individual toxicity profiles of the constituent agents.

RVd: adverse events and management

AE reported with RVd are generally consistent with the

profiles of lenalidomide and bortezomib combined with dexamethasone, and include thrombocytopenia, neutropenia, infection, and PN.[15,55] Multiple AE prevention strategies are relevant for RVd in clinical practice. RVd is likely to induce emesis in some patients (<30%); therefore, antiemetic prophylaxis can be given on bortezomib treatment days, as needed.[56] Optimal use of granulocyte colony-stimulating factor prophylaxis in this population is dynamic, and it may be considered for neutropenia management. Antiviral prophylaxis is considered mandatory against varicella zoster, while antibacterial prophylaxis is recommended for some patients based on their individual risk factors. Thromboprophylaxis is mandatory unless contraindicated. Other strategies as supportive care may also ameliorate toxicities, including emollients and supplements for treatment-emergent PN or infusion of normal saline during bortezomib administration.[57]

Stem cell collection following RVd induction is an important consideration for patients who can later pursue ASCT. [28-30,34,49] Stem cell collection should be completed within four to six cycles of RVd induction therapy.[58]

RVd: dose and schedule

The posology of RVd is critical to optimize effectiveness. Reduced dose intensity via modifying cycle length and dosing frequency can attenuate the risk or severity of AE. Appropriate dose modifications (i.e., interruptions, reductions, or discontinuations) are key for AE management after onset.[57] Importantly, the use of SC rather than IV bortezomib can reduce the intensity and frequency of PN without compromising efficacy.[59] If discontinuation of bortezomib is warranted, Rd may be continued until progressive disease. RVd has been administered in varying posologies (Table 2), leading to nomenclature that reflects varying schedules of dose intensity which we will use throughout this review:

- "RVd Classic": 21-day cycle, lenalidomide 25 mg (days 1-14), bortezomib 1.3 mg/m^2 (days 1, 4, 8, 11), dexamethasone 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12)
- "RVd Lite": 35-day cycle, lenalidomide 15 mg (days 1-21), bortezomib 1.3 mg/m^2 (days 1, 8, 15, 22), dexamethasone 20 mg (≤75 years of age: days 1, 2, 8, 9, 15, 16, 22, 23; >75 years of age: days 1, 8, 15, 22)

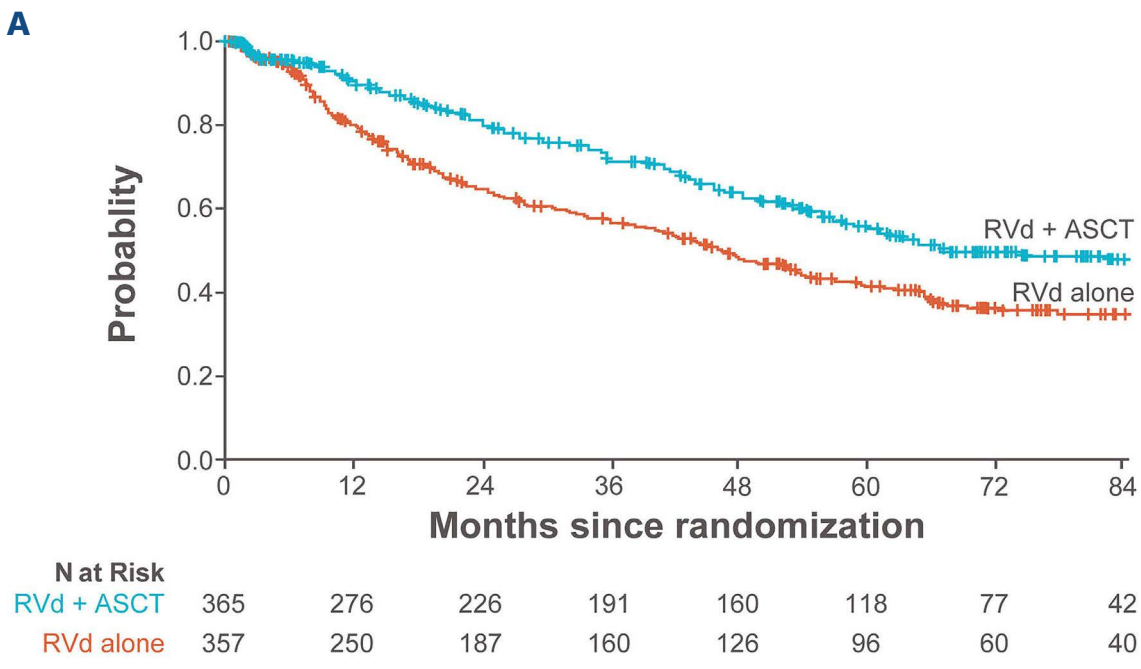

Figure 2. Progression-free survival and overall survival for RVd + autologous stem cell transplant *versus* RVd alone in the DETERMINATION trial (median follow-up, 76.0 months). (A) Progression-free survival. (B) Overall survival. Figures from the New England Journal of Medicine, Richardson PG, *et al.*, "Triplet therapy, transplantation, and maintenance until progression in myeloma".[45] Copyright© (2022) Massachusetts Medical Society. Reprinted with permission. ASCT, autologous stem cell transplant; RVd, lenalidomide, bortezomib, and dexamethasone.

- "RVd Ultralite": 28- to 35-day cycle, lenalidomide 15 mg (days 1-21), bortezomib 1.3 mg/m^2 (days 1, 8, 15), dexamethasone 20 mg (days 1, 2, 8, 9, 15, 16)
- "RVd Premium Lite": 28-day cycle, lenalidomide 25 mg (days 1-21), bortezomib 1.3-1.6 mg/m^2 (days 1, 8, 15, 22), dexamethasone 20 mg (days 1, 2, 8, 9, 15, 16, 22, 23)
- "GEM-RVd": 28-day cycle, lenalidomide 25 mg (days 1-21), bortezomib 1.3 mg/m^2 (days 1, 4, 8, 11), dexamethasone 40 mg (days 1-4, 9-12)

The use of these names remains fluid. VRd, which is sometimes used as an alternate, describes the steroid-attenuated regimen first developed in the EVOLUTION trial. The distinctions otherwise center on cycle length and bortezomib frequency. Most commonly, RVd was administered in 21-day cycles, with lenalidomide 25 mg on days 1-14 and bortezomib 1.3 mg/m^2 (IV or SC) on days 1, 4, 8, and 11; some studies used dexamethasone 40 mg once weekly,[29,30] and others split the dose to 20 mg on days of and after bortezomib ("partnered dosing", totaling 80 mg/week).[32,33,37,41,43] Importantly, although weekly dexamethasone may be more convenient for some patients, the severity of bortezomib-induced PN may be mitigated by partnered dosing.[60]

PETHEMA/GEM2012 used 28-day cycles,[49] which provide higher lenalidomide and dexamethasone dose intensities and a lower bortezomib dose intensity compared with 21-day regimens, which may allow for increased efficacy and completion of planned induction.

RVd Lite was developed specifically to maximize tolerability in older patients by extending cycle length, reducing the lenalidomide dose, administering bortezomib SC once weekly four times, and using an age-based schedule for dexamethasone.[31] RVd Lite has the lowest lenalidomide intensity of all reviewed regimens, but offers long-term lenalidomide treatment (9 RVd induction cycles, 6 lenalidomide + bortezomib consolidation cycles, and optional lenalidomide maintenance) and demonstrates striking activity, less toxicity, and impressive clinical benefit.[15,61]

A recent observational, single-center study evaluated another modified version of RVd in TE NDMM, using full-dose lenalidomide and once-weekly bortezomib with the goal of minimizing PN risk.[62] Patients received induction or salvage therapy with lenalidomide 25 mg on days 1-21; bortezomib 1.3 mg/m^2 SC on days 1, 8, and 15; and dexamethasone 40 mg on days 1, 8, and 15 (28-day cycles). The overall response rate (ORR) was 87%, and 63% of patients achieved ≥VGPR. Of note, those who received RVd for induction had an ORR of 89% compared to 75% in those who received salvage, with no cases of grade ≥3 PN.

To date, there are no head-to-head comparisons of the various RVd dosing regimens, and thus the advantages of any one regimen over another are not definitive. Although data from single-center studies support weekly bortezomib use,[63] selection of this schedule should be individualized based on risks and benefits. Moreover, additional data reported across numerous studies with different patient populations allow clinicians considerable flexibility to factor in patient- and disease-specific factors when selecting the RVd dose and schedule, although most patients receive RVd Classic dosing regimens.[64,65]

RVd and quadruplet regimens

Given its proven efficacy, RVd has been used as a foundation for quadruplet regimens for the treatment of NDMM. The first study of an RVd-based quadruplet was the previously discussed EVOLUTION trial, which included a VRd + cyclophosphamide (VRdC) arm.[29] The efficacy of VRdC and VRd was similar (ORR, 88% *vs*. 85%; 1-year PFS rates, 86% and 83%). Hematologic toxicity rates were higher with VRdC than with VRd, especially grade 3/4 neutropenia (44% *vs*. 10%) and leukopenia (13% *vs*. 0%), with treatment-related mortality in the VRdC arm. Additionally, a phase I/II study investigated RVd + pegylated liposomal doxorubicin in eight 21-day cycles.[66] Patients achieving ≥PR after four cycles could proceed to ASCT, and those achieving stable disease or better after eight cycles and not proceeding to ASCT could receive RVd maintenance. The phase II dose used RVd Classic, with dexamethasone 10 mg in cycles 5-8 and pegylated liposomal doxorubicin 30 mg/m^2 on day 4: the ORR after four and eight cycles was 96% and 95%, with ≥VGPR in 57% and 65%, respectively. The median PFS was NR, but 18-month PFS was 81.6%, with grade 3/4 neutropenia and thrombocytopenia reported in 19% and 11% of patients, respectively. Results of these trials suggest that conventional chemotherapy may not be the ideal addition to RVd.

Conversely, in the previously described phase II GRIFFIN study, patients with TE NDMM received either RVd or RVd-DARA.[34] The rates of grade 3/4 neutropenia and thrombocytopenia were higher with RVd-DARA than with RVd; however, rates of grade 3/4 lymphopenia and PN were similar. A final analysis of the safety run-in cohort of the GRIFFIN study found that 15 (93.8%) of the 16 patients receiving RVd-DARA achieved a stringent CR as best response at last follow-up.[67] Additionally, the phase III COLUMBA RRMM trial has demonstrated non-inferiority of SC *versus* IV daratumumab, with an improved safety profile.[68] The phase II PLEIADES study examined the addition of SC daratumumab to standard-of-care regimens and found that SC daratumumab had comparable efficacy to IV daratumumab (≥VGPR of 71.6% for RVd-DARA, ORR of 88.1% for VMP-DARA, ORR of 90.8% for Rd-DARA), with a median infusion duration of only 5 minutes and a low rate (≤9%) of infusion-related reactions.[69] The ongoing phase III NDMM studies MMY3019 (NCT03652064) and PERSEUS (NCT03710603) are evaluating RVd-DARA *versus* RVd using SC daratumumab in patients not planned to undergo ASCT and in TE patients,

respectively. Of note, the PERSEUS study used a regimen of oral lenalidomide 25 mg on days 1-21 and oral dexamethasone 40 mg on days 1-4 and days 9-12 of each 28-day induction cycle. Additionally, the ongoing phase II MMY2040 study is evaluating multiple daratumumab-containing regimens (including RVd-DARA) using the SC formulation (NCT03412565).

In the phase I portion of SWOG S1211, elotuzumab + RVd demonstrated limited additive toxicity to RVd alone.[70] However, in the randomized phase II portion in high-risk NDMM, elotuzumab + RVd did not significantly improve patients' outcomes compared to RVd alone (ORR=83% *vs*. 88%; median PFS, 31 *vs*. 34 months).[71] This finding was supported in a follow-up analysis of RVd + elotuzumab *versus* RVd in SWOG-1211, with no improvement in median PFS (29 *vs*. 34 months) or OS (NR *vs*. 68 months) observed with a median follow-up of 6 years.[71] Another phase II trial of patients with TE NDMM demonstrated an ORR (after 4 cycles) of 82.5%, with 55.0% of patients achieving ≥VGPR.[72] However, 50% of patients experienced infections, including one grade 5 sepsis. In the phase III GMMG HD6 trial, four induction cycles of elotuzumab + RVd produced similar response outcomes as RVd alone (ORR, 82.4% *vs*. 85.6%; ≥VGPR, 58.3% *vs*. 54.0%).[73] Isatuximab + RVd was well tolerated in a phase I study and extremely active,[74] with phase I (NCT02513186), phase II/III (UK-MRA Myeloma XV RADAR [2019-001258-25]), and phase III (GMMG-HD7 [NCT03617731] and IMROZ [NCT03319667]) NDMM clinical trials ongoing.[75] Notably, the combination of panobinostat + RVd demonstrated activity and tolerability in a phase Ib study of patients with RRMM[76] and favorable efficacy in a phase Ib study of TE NDMM patients.[77] In the TE NDMM study, patients who received panobinostat + RVd at the maximum tolerated dose (RVd Classic with SC bortezomib and panobinostat 10 mg on days 1, 3, 5, 8, 10, and 12) had an ORR of 96% after ≤4 cycles, including a ≥VGPR rate of 87%.[77] The toxicity of panobinostat + RVd manifested as primarily low-grade gastrointestinal effects, which were usually manageable with supportive care. Finally, in a phase I trial of vorinostat + RVd in NDMM, vorinostat proved most tolerable at 200 mg given on days 1-14 of each 21-day cycle with the RVd Classic regimen.[78] An objective response was observed in 96% of patients, with 48% of patients achieving complete remission.[78] Gastrointestinal symptoms (87%), fatigue and PN (60%), and thrombocytopenia (33%) were the most common AE.[78]

In summary, RVd-based quadruplet regimens with monoclonal antibodies have exhibited promising activity and tolerability, although data from patients with high-risk MM remain limited, and demonstrate the clinical potential of RVd as a foundation for four-drug regimens. Importantly, toxicity profiles were not additive and proved manageable.

Perspective

Although multiple triplet regimens have been explored in the NDMM setting (Table 4), RVd is a particularly attractive option. RVd has been extensively evaluated in phase II and III trials, demonstrating impressive clinical activity, deep and durable responses in both TE and TNE NDMM populations, and a manageable safety profile. Moreover, the variety of dosage schedules investigated, including both high- and low-dose intensity modifications to the common 21-day cycles, facilitate unique customization for clinicians who may want to emphasize deep responses or tailored tolerability and treatment duration. Additionally, the improvement in median PFS observed with RVd + ASCT in frontline treatment, particularly in high-risk patients, demonstrates how RVd can be used as a platform to build patient-tailored treatments and reaffirms early-line ASCT as a standard of care in selected patients.[45] This benefit of RVd as a backbone regimen in high-risk patients was further supported by the results of the UK Optimum/MUKnine trial, which reported a 94% ORR at the end of induction and an 83% ORR at day 100 after ASCT in ultra-high-risk patients with NDMM.[79]

Thus, RVd has become a standard of care in NDMM. Global treatment guidelines (including those in the USA and EU) recommend RVd regardless of transplant eligibility.[1,2] A *post-hoc* subgroup analysis of SWOG S0777 suggesting a smaller magnitude of benefit with RVd in older patients (≥65 years) is a consideration; however, further study in this population is needed. Recent approvals will likely increase the use of RVd in clinical practice, particularly in the EU. The availability of generic bortezomib and lenalidomide will also likely reduce the cost associated with induction therapy and contribute to increased use in real-world practice. Moreover, the excellent activity of RVd has been confirmed outside of the clinical trial setting.[65] The RVD 1000 study, a database cohort study of 1,000 patients with NDMM who received RVd induction ± ASCT and risk-adapted maintenance, reported an ORR of 97.1% after induction (≥VGPR, 67.6%; ≥CR, 35.9%), a median PFS of 65.0 months, and a median OS of 126.6 months, demonstrating the substantial long-term benefit of RVd. The large size of the study enables subanalyses, including for standard- *versus* high-risk cytogenetics (median PFS, 76.5 *vs*. 40.3 months; median OS, NR *vs*. 78.2 months, respectively).

In the context of the TE NDMM population, the recent results of DETERMINATION, with its relative maturity of follow-up, provide insights into the benefit of RVd in different populations and validate the tailoring of treatment in each individual patient, based upon the outcomes reported.[45-47] The comparisons between DETERMINATION and IFM/DFCI 2009 further validate the importance of lenalidomide maintenance until progression after RVd-based induction

as well as the benefit and competing risks of the use of high-dose melphalan with its impact on OS.[43-45] The next steps in improving outcomes are well underway and include the integration of monoclonal antibodies and other

Table 4. Phase III induction data from select non-RVd-based triplet regimens for newly diagnosed multiple myeloma.

Regimen	Study	Population	Response	PFS and OS	Selected safety findings
VMP	VISTA[88,89] (NCT00111319) 9 × 42-day cycles of VMP (IV BORT)	N=344 (N=337, response; N=340, safety) TNE patients	ORR: 74.5% ≥VGPR: 41.2% ≥CR: 32.9%	Median TTP: 24.0 mths 3-yr OS rate: 68.5%	Grade 3/4 AE Neutropenia: 40.0% Thrombocytopenia: 37.1% Leukopenia: 22.6% Lymphopenia: 19.7% Anemia: 18.2% PN: 12.9%
VMP	GIMEMA-MM-03-05[90,91] (NCT01063179) 9 × 42-day cycles of VMP (IV BORT)	N=257 (N=253, response/safety) TNE patients	ORR: 81.0% ≥VGPR: 49.8% ≥CR: 24.1%	Median PFS: 24.8 mths Median OS: 60.6 mths	Grade 3/4 AE Neutropenia: 28.1% Thrombocytopenia: 19.8% PN: 5.1%
VMP	UPFRONT[92] (NCT00507416) 8 × 21-day cycles of VMP (IV BORT) → 5 × 35-day cycles of BORT maintenance	N=167 (N=145 response; N=163 safety) TNE patients	Induction response: ORR: 67.6% ≥VGPR: 36.6% ≥CR: 2.8%	Median PFS: 17.3 mths Median OS: 53.1 mths	Grade ≥3 AE PN: 19.6% Neutropenia: 19.0% Infection: 17.8% Thrombocytopenia: 14.7% Grade ≥2 PN: 35.0%
VMP	ALCYONE[93,94] (NCT02195479) 9 × 42-day cycles of VMP (SC BORT)	N=356 TNE patients	ORR: 73.9% ≥VGPR: 49.7% ≥CR: 25.3%	Median PFS: 19.3 mths 36-mth OS rate: 67.9%	Grade 3/4 AE Neutropenia: 38.7% Thrombocytopenia: 37.6% Anemia: 19.8% Infections: 14.7% PN: 4.0%
VMP	CLARION[95] (NCT01818752) 9 × 42-day cycles of VMP (IV or SC BORT)	N=477 (N=470, safety) TNE patients	ORR: 78.8% ≥VGPR: 49.3% ≥CR: 23.1%	Median PFS: 22.1 mths	Grade ≥3 AE Neutropenia: 29.4% Thrombocytopenia: 21.1% Anemia: 13.6% Leukopenia: 12.8% PN: 7.9%
VTD	GIMEMA MMY-3006[51,96] (NCT01134484) 3 × 21-day cycles of VTD (IV BORT) → tandem ASCT → consolidation with 2 × 35-day cycles of VTD → DEX maintenance	N=236 TE patients	Induction response: ORR: 93.2% ≥VGPR: 61.9% ≥CR: 18.6%	10-yr PFS rate: 34% 10-yr OS rate: 60%	Grade 3/4 AE during induction Skin rash: 10.2% PN: 9.7%
VTD	IFM 2007-02[97] (NCT00910897) 4 × 21-day cycles of VTD (reduced dose THAL/IV BORT) → ASCT (post-ASCT treatment at physician discretion)	N=100 TE patients	Induction response: ORR: 88% ≥VGPR: 49% ≥CR: 13%	Median PFS: 26 mths	Grade 3/4 AE during induction Infections: 10.0% PN: 3.0%
VTD	GEM2005[54] (NCT00461747) 6 × 28-day cycles of VTD (IV BORT) → ASCT → maintenance (IFN-α2b *vs.* VT)	N=130 TE patients	Induction response: ORR: ≈85% ≥VGPR: ≈60% ≥CR: 35%	Median PFS: 56.2 mths 4-yr OS rate: 74%	Grade 3/4 AE during induction Infection 20.8% PN: 13.1% DVT/PE: 11.5% Neutropenia: 10.0%

Continued on following page.

Regimen	Study	Population	Response	PFS and OS	Selected safety findings
VTD	IFM 2013-04[53] (NCT01564537) 4 × 21-day cycles of VTD (SC BORT) → ASCT (conditioning regimen, single *vs.* tandem ASCT, consolidation, maintenance at discretion of each center)	N=169 (ITT) TE patients	Induction response: ORR: 92.3% ≥VGPR: 66.3% ≥CR: 13.0%	Not evaluated	Grade 3/4 AE during induction Neutropenia: 18.9% Grade 2-4 PN: 21.9%
VTD	CASSIOPEIA[98] (NCT02541383) 4 × 28-day cycles of VTD (SC BORT) → ASCT → 2 × 28-day cycles of VTD → maintenance (DARA *vs.* observation)	N=542 (N=538, safety) TE patients	Induction response: ORR: 89.9% ≥VGPR: 56.1% ≥CR: 8.9%	18-mth PFS rate: 85%	Grade 3/4 AE Stomatitis: 16.4% Neutropenia: 14.7% PN: 8.6%
VTD	UPFRONT[92] (NCT00507416) 8 × 21-day cycles of VTD (IV BORT) → 5 × 35-day cycles of BORT maintenance	N=167 (N=133 response; N=158 safety) TNE patients	Induction response: ORR: 78.9% ≥VGPR: 48.9% ≥CR: 0.8%	Median PFS: 15.4 mths Median OS: 51.5 mths	Grade ≥3 AE PN: 27.2% Infection: 15.8% Fatigue: 12.0% Grade ≥2 PN: 47.5%
CyBorD	GMMG-MM5[99] 3 × 21-day cycles of CyBorD → ASCT (single or tandem) → 2 cycles LEN consolidation → LEN maintenance[a]	N=251 (ITT); (N=250, safety) TE patients	Induction response: ORR: 78.1% ≥VGPR: 37.1%	Not reported	Grade ≥3 AE during induction Leukocytopenia/neutropenia: 35.2% Grade ≥2 AE Infections and infestations: 22.4% Neuropathy: 8.4%
CyBorD	IFM2013-04[53] (NCT01564537) 4 × 21-day cycles of CyBorD (SC BORT) → ASCT (conditioning regimen, single *vs.* tandem ASCT, consolidation, maintenance at discretion of each center)	N=169 (ITT) TE patients	Induction response: ORR: 83.4% ≥VGPR: 56.2% ≥CR: 8.9%	Not evaluated	Grade 3/4 AE during induction Neutropenia: 33.1% Thrombocytopenia: 10.6% Infection: 10.1% Grade 2-4 PN: 12.9%
RAD	DSMM XIV[41,42] (NCT01685814) 3 × 28-day cycles of RAD → response adapted SCT and LEN maintenance	N=232 TE patients	Induction response: ≥CR: 13.5% ≥VGPR: 40.6%	Median PFS (from first randomization) RAD: 41.7 mths	Grade ≥3 AE Neutropenia: 6.5% PN/neuralgia: 0%
DRd	MAIA[26,100] (NCT02252172) 28-day cycles of DRd until PD or unacceptable toxicity	N=368, (N=364 for safety) TNE patients	ORR: 92.9% ≥VGPR: 80.7% ≥CR: 51.1%	48-mth PFS rate: 60%	Grade 3/4 AE Neutropenia: 53.3% Pneumonia: 18.4% Anemia: 16.2% Lymphopenia: 16.2% Infections: 40%
KRd	ENDURANCE[40] (E1A11) (NCT01863550) 9 × 28-day cycles of KRd → LEN maintenance × 2 years *vs.* LEN maintenance until PD	N=545 (N=526 for ORR, safety) Patients not planned for early ASCT	Induction response: ORR: 86.7% ≥VGPR: 73.8% ≥CR: 18.3%	Median PFS: 34.6 mths 3-year OS rate: 86%	Grade 3/4 AE Dyspnea: 7.2% Hyperglycemia: 6.5% PN: 0.8% Grade ≥3 cardiac, pulmonary, and renal AE: 16.0%

Data are provided for informational purposes only. No cross-trial comparisons should be made. Differences in patient population, study design (length of induction; use of transplant, consolidation, and/or maintenance), assessment criteria, and/or study conduct may have an impact on the results of each trial. [a]Bortezomib was changed from intravenous to subcutaneous during the trial. AE: adverse effects; ASCT:autologous stem cell transplant; BORT: bortezomib; CR: complete response; CyBorD: cyclophos-

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phamide, bortezomib, and dexamethasone; DARA: daratumumab; DEX: dexamethasone; DRd: daratumumab, lenalidomide, and dexamethasone; DVT: deep vein thrombosis; IFN: interferon; ITT: intent-to-treat; IV: intravenously; KRd: carfilzomib, lenalidomide, and dexamethasone; LEN: lenalidomide; ORR: overall response rate; OS: overall survival: PD: disease progression; PE: pulmonary embolism; PFS: progression-free survival; PN: peripheral neuropathy; RAD: lenalidomide, adriamycin, and dexamethasone; RVd: lenalidomide, bortezomib, and dexamethasone; SC: subcutaneously; TE: transplant eligible; THAL: thalidomide; TNE: transplant ineligible; TTP: time to progression; VCD: bortezomib, cyclophosphamide, and dexamethasone; VGPR: very good partial response; VMP: bortezomib, melphalan, and prednisone; VT: bortezomib and thalidomide; VTD: bortezomib, thalidomide, and dexamethasone; mth/mths: month/months; yr: year.

novel strategies to enhance the effectiveness of treatment paradigms in NDMM.[46,47]

In consideration of RVd, the potent activity of the second-generation proteasome inhibitor carfilzomib is fully acknowledged. Unlike RVd, carfilzomib + Rd (KRd) is approved only in the RRMM setting. In the USA, KRd is indicated for the treatment of patients with RRMM after one to three prior lines of therapy, and in the EU, KRd is approved for use in patients with RRMM after one or more prior lines of therapy. Regulatory approval of KRd for RRMM was based on findings from the phase III ASPIRE trial,[80] which led to the clinical investigation of KRd in TE NDMM patients in the randomized phase II FORTE trial.[81] Patients were randomized to either 12 cycles of KRd (KRd12); KRd followed by ASCT and KRd consolidation (KRd + ASCT); or carfilzomib, cyclophosphamide, and dexamethasone (KCd) followed by ASCT and KCd consolidation (KCd + ASCT). Both KRd regimens resulted in deep responses, with pre-maintenance ≥CR rates of 52% (KRd12) and 49% (KRd + ASCT), and MRD-negativity rates of 54% and 58%, respectively. KRd has also been evaluated as a basis for quadruplet regimens; KRd + daratumumab in the phase Ib MMY1001 trial in NDMM showed a tolerability profile consistent with KRd and very promising response rates.[82] Although the depth of response conferred by KRd is profound, interim results of the phase III ENDURANCE (E1A11) NDMM study evaluating RVd *versus* KRd in patients with standard-risk MM demonstrated similar efficacy of the two regimens.[40]

Clinicians must also consider toxicity when evaluating proteasome inhibitors. In addition to thrombocytopenia,[76] the most commonly reported AE are PN for bortezomib and cardiovascular, renal, thromboembolic, and pulmonary toxicities for carfilzomib. Bortezomib-associated PN can be debilitating and lead to the interruption or cessation of treatment, but the use of SC bortezomib as well as supportive measures and modified RVd regimens have alleviated much of this risk.[31,59] Carfilzomib is associated with a much lower rate of PN than bortezomib, but confers an increased risk of potentially life-threatening cardiovascular toxicity.[83] A systemic review and meta-analysis of carfilzomib-associated cardiovascular toxicity demonstrated an estimated cumulative incidence of 5% for grade ≥3 toxicity.[84] Furthermore, concomitant use of carfilzomib and an immunomodulatory agent was found to significantly increase the risk of cardiovascular toxicity compared to that of carfilzomib without an immunomodulatory agent (6.45% *vs*. 4.34%; P=0.033). Notably, the incidence of cardiotoxicity was similar with high and standard doses of carfilzomib, although another systemic review and meta-analysis concluded that cardiovascular AE rates were higher with carfilzomib doses ≥45 mg/m^2.[83,84] In contrast, the bortezomib-associated risk of PN is known to be dose-dependent, and can be ameliorated by dose reductions and schedule changes.[31,59,60] Interim findings from the phase III ENDURANCE study provide crucial comparative safety data between the regimens: rates of grade ≥3 cardiac, pulmonary, and renal TEAE were lower with RVd than with KRd (P<0.0001), while rates of grade 3/4 PN were higher with RVd than with KRd.[40] Rates of overall grade ≥3 serious AE were lower with RVd (P=0.038).

Similar considerations when selecting front-line regimens for TE or TNE NDMM patients are overall toxicity and impact on quality of life relative to survival benefit. In DETERMINATION, a robust PFS benefit was noted with RVd + ASCT *versus* RVd, but patients treated with RVd + ASCT had greater rates of grade ≥3 treatment-related AE and transient but meaningful decreases in quality of life.[45] In the absence of an OS benefit and the availability of multiple efficacious combination therapies for NDMM, patients and healthcare providers will need to consider the benefits of adding ASCT to regimens for TE NDMM patients relative to the risk of toxicity and impact on quality of life. This consideration provides a unique opportunity to tailor treatment regimens to a given patient's characteristics, lifestyle, cytogenetic risk profile, and treatment goals while still inducing deep and durable responses.[45]

Personalized decision-making for patients regarding treatments is essential in the NDMM setting. Given the positive prognostic value of MRD status for patients' outcomes, MRD status is increasing in clinical relevance. In a preliminary analysis of MRD status in DETERMINATION, a greater proportion of patients were MRD-negative with RVd + ASCT than with RVd alone, and patients with MRD-negative status had longer median PFS compared with patients with MRD-positive status.[45] However, PFS was similar in patients receiving RVd or RVd + ASCT in whom no MRD was detected, suggesting that treatment adaptation based upon MRD status may be a potential alternative to the current paradigm of ASCT use, although further trials will be required to fully understand the interaction of MRD status with optimal duration of therapy.[45]

A final point of discussion is subsequent therapy following induction and relapse as a strategic consideration. Pa-

tients may benefit from purposeful preservation of highly effective agents until after initial progressive disease, since management of early relapse is another crucial juncture in a patient's treatment journey.[7] Frontline use of RVd (or an RVd-containing quadruplet regimen), bolstered by the well-established clinical profile and improved manageability of RVd, represents an attractive initial intervention. This facilitates longer-term treatment with RVd until progressive disease in the TNE NDMM population or completion of intended induction in TE NDMM patients. Using RVd in this setting also secures the option of using carfilzomib- and pomalidomide-containing regimens at early relapse. Either approach has been associated with impressively deep responses and broad efficacy in RRMM, which can be complemented by a monoclonal antibody, further improving long-term outcomes.[45,85,86] The development of novel alkylating agents, such as melflufen, and novel cellular therapeutics, such as chimeric antigen receptor T cells, cereblon E3 ligase modulatory drugs, and bispecific T-cell engagers, may further help to tailor treatments and diversify options available for patients who are refractory to certain agents or drug classes.[87]

Given the robust body of data in clinical trials across multiple settings, increasing physician familiarity with RVd, and the evolving maturity of promising data regarding RVd-containing quadruplet regimens, RVd is established as a foundation of NDMM combination therapy with consistent clinical benefit now and into the future.

Disclosures

PGR reports serving on advisory committees for Karyopharm, Oncopeptides, Celgene, a Bristol-Myers Squibb Company, Takeda, Janssen, GSK, Regeneron, and AstraZeneca, and has received research funding from Oncopeptides, Celgene, a Bristol-Myers Squibb Company, Takeda, and Karyopharm. AD reports serving on advisory committees for Janssen and Alnylam Pfizer, Takeda, and Bristol Myers Squibb, and has received research funding from Bristol Myers Squibb. LR reports honoraria from Janssen, Celgene, a Bristol-Myers Squibb Company, Amgen, Takeda, Sanofi, GSK, and Karyopharm. EO reports serving on advisory boards for Bristol Myers Squibb, Takeda, Karyopharm, Adaptive, Oncopeptides, and Janssen. TF reports serving on advisory committees for Janssen, Bristol Myers Squibb, Takeda, Amgen, Roche, Oncopeptides, Karyopharm, and AbbVie. MVM has received honoraria and speakers bureau compensation from Janssen, Celgene, a Bristol-Myers Squibb Company, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Adaptive, Sanofi, Oncopeptides, Seagen, Roche, and bluebird bio. PM has received honoraria from Amgen, Celgene, a Bristol-Myers Squibb Company, Janssen, AbbVie, Sanofi, Oncopeptides, and GSK. NR reports consultancy for Amgen, Bristol Myers Squibb, Janssen, and Takeda. NM reports consultancy for Adaptive Biotech, Amgen, Bristol Myers Squibb, Janssen, Karyopharm Therapeutics, Legend, OncoPep, and Takeda; and reports stock ownership with OncoPep. PV reports serving on advisory boards for Adaptive Biotechnologies, Bristol Myers Squibb, Janssen, and Teneobio; has served in a consultancy role for Novartis and Oncopeptides; and has received honoraria from GSK and Oncopeptides. JB has received honoraria from Celgene, a Bristol-Myers Squibb Company, Janssen, and Amgen. SL reports consultancy for AbbVie, Bristol Myers Squibb, Celgene, a Bristol-Myers Squibb Company, GSK, Janssen, Karyopharm, Novartis, and Takeda. AP has received research funding from Takeda and honoraria from AbbVie, Amgen, Bristol Myers Squibb, Celgene, a Bristol-Myers Squibb Company, Janssen, Sanofi, and Takeda. KCA reports serving on advisory boards for Celgene, a Bristol-Myers Squibb Company, Millennium, Janssen, Sanofi, Bristol Myers Squibb, Gilead Sciences, Precision Biosciences, and Tolero, as well as being the Scientific Founder of OncoPep and C4 Therapeutics. BGD, SK, JPL, and PO have no conflicts of interest to disclose.

Contributions

The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version that reflects the authors' interpretations and conclusions.

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