

## REVIEW

# Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group

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The prognosis for patients multiple myeloma (MM) has improved substantially over the past decade with the development of new, more effective chemotherapeutic agents and regimens that possess a high level of anti-tumor activity. In spite of this important progress, however, nearly all MM patients ultimately relapse, even those who experience a complete response to initial therapy. Management of relapsed MM thus represents a vital aspect of the overall care for patients with MM and a critical area of ongoing scientific and clinical research. This comprehensive manuscript from the International Myeloma Working Group provides detailed recommendations on management of relapsed disease, with sections dedicated to diagnostic evaluation, determinants of therapy, and general approach to patients with specific disease characteristics. In addition, the manuscript provides a summary of evidence from clinical trials that have significantly impacted the field, including those evaluating conventional dose therapies, as well as both autologous and allogeneic stem cell transplantation. Specific recommendations are offered for management of first and second relapse, relapsed and refractory disease, and both autologous and allogeneic transplant. Finally, perspective is provided regarding new agents and promising directions in management of relapsed MM.

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## INTRODUCTION

Multiple myeloma (MM) is a B-cell neoplasm characterized by aberrant expansion of plasma cells, typically within the bone marrow but increasingly in extramedullary sites with disease progression.<sup>1</sup> Induction regimens incorporating thalidomide, lenalidomide and/or bortezomib are now standard for newly diagnosed MM.<sup>2–6</sup> Eligible patients may undergo autologous stem cell transplantation (ASCT), which deepens and prolongs the therapeutic response and improves outcome, especially when integrated with novel agents.<sup>7–9</sup> Consolidation/maintenance post-ASCT not only upgrades but also deepens the response which translates into improved progression-free survival (PFS).<sup>10,11</sup> Current approaches to management of newly diagnosed MM have significantly increased survival in MM.<sup>12,13</sup> However, even patients who achieve a high quality and prolonged duration of response with initial therapy will ultimately relapse.

Thus, management of relapsed disease is a critical aspect of MM management and an important focus of ongoing research.

## DEFINITIONS AND DIAGNOSIS OF RELAPSED/REFRACTORY AND PROGRESSIVE MM

### Definitions

Progressive MM is defined as a 25% increase from baseline in the serum monoclonal protein (M-protein; absolute increase  $\geq 0.5$  g/dl), urine M-protein (absolute increase  $> 200$  mg/day), percentage of bone marrow plasma cells (absolute percentage increase  $> 10\%$ ), and/or the difference between involved and uninvolved free light chain levels (absolute increase must be  $> 10$  mg/dl).<sup>14</sup> Progressive disease can also be established based on the presence of definite new bone lesions and/or soft tissue plasmacytomas, with a clear increase in the size of existing

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plasmacytomas, or hypercalcemia, that cannot be attributed to another cause.

Disease that meets these criteria for progression is defined as relapsed disease. Relapsed and refractory MM, meanwhile, is defined as disease that progresses on salvage therapy or progresses within 60 days of the last treatment in patients who previously achieved at least a minimal response (MR) to treatment.

These entities are distinguished from primary refractory MM, which refers to disease that fails to achieve at least an MR with any therapy. It is also important to note that following ASCT, oligoclonal reconstitution may occur which is temporary and does not indicate relapse.<sup>15</sup>

**Diagnostic evaluation**

The diagnostic evaluation includes serum protein electrophoresis with immunofixation, 24-h urine for both total protein and urine protein electrophoresis with immunofixation, and the serum-free light chain assay. A comprehensive metabolic panel is obtained with attention to renal function, calcium concentration and other metabolic abnormalities. A complete blood count with differential is obtained to assess for cytopenias as well as the presence of circulating plasma cells. The  $\beta_2$  microglobulin is usually obtained, as recent analyses suggest value in assessing this parameter prognostically in the context of disease relapse.<sup>16</sup>

Bone marrow evaluation is considered a standard of care when evaluating relapsed MM, though on some occasions may not be necessary, if disease progression is clearly confirmed by serum protein electrophoresis/urine protein electrophoresis and/or serum-free light chain. Bone marrow evaluation should be performed in cases of non- or oligo-secretory disease as well as when a secondary bone marrow process such as myelodysplasia is suspected. When bone marrow evaluation is undertaken, repeat fluorescence *in situ* hybridization analysis (with CD138 selection of clg *in situ* hybridization) should be performed, since new chromosomal abnormalities may be identified, with possible exceptions in cases where high-risk cytogenetic features had been previously identified.

Imaging with either skeletal survey, magnetic resonance imaging or, in selected cases, fluorodeoxyglucose-positron emission tomography is conducted to assess for new sites of disease, an increase in previous areas of involvement or the presence of extramedullary disease.

**DETERMINANTS OF THERAPY**

In undertaking the diagnostic evaluation, it is important to consider various factors that will influence treatment strategy (Figure 1). These include characteristics of the disease itself, response and duration of response (DOR) to prior therapy including treatment-related toxicities, eligibility for stem cell transplantation and characteristics of the individual patient.

**Disease characteristics**

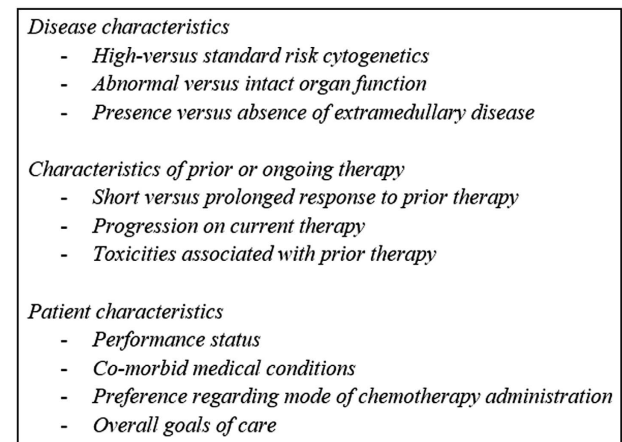
Relapsed MM may manifest as biochemical progression based on an increase in the paraprotein concentration, with no associated symptoms or MM-related organ dysfunction. In other cases, progressive disease develops with prominent symptoms and/or significant organ compromise such as cytopenias, bone or soft tissue plasmacytomas, hypercalcemia, or renal failure.

High-risk relapsed disease is defined by any of the following characteristics (Table 1).

1. Adverse cytogenetic abnormalities (hypodiploidy, t(4;14), del(17p), amp(1q21).
2. High B2M (> 5.5 mg/l) or low albumin (< 3.5 mg/dl).

3. The presence of extramedullary disease.
4. Short DOR to prior therapy or progression while on current therapy.
5. Aggressive clinical features including.
  - Rapid onset of clinical symptoms
  - Extensive disease at relapse based on laboratory, pathology, or radiographic findings
  - Disease-associated organ dysfunction at relapse including renal failure, hypercalcemia or bone event such as fracture
7. High LDH.
8. Circulating plasma cells.

As in newly diagnosed disease, adverse cytogenetic abnormalities detected at relapse portend a poor outcome.<sup>17,18</sup> High-risk chromosomal abnormalities such as del(17p) may be detected in a patient who previously had standard-risk MM. A patient with high-risk cytogenetics at diagnosis retains that designation throughout the disease course.



**Figure 1.** Determinants of therapy in relapsed or relapsed/refractory MM multiple myeloma.

**Table 1.** High-risk disease characteristics in relapsed and/or relapsed-refractory MM

<i>Disease related parameters</i>		
Adverse cytogenetic abnormalities	del(17p), amp(1q21) or t(4;14)	Dimopoulos et al. <sup>18</sup> Smetaneet et al. <sup>115</sup> Jakubowiak et al. <sup>116</sup> Reece et al. <sup>117</sup>
Extramedullary disease		Rasche et al. <sup>118</sup> Dimopoulos et al. <sup>18</sup> Papanikolaou et al. <sup>119</sup>
Short remission duration after first treatment		Sellner et al. <sup>120</sup> Jimenez-Zepeda et al. <sup>121</sup>
ISS stage at relapse		Sellner et al. <sup>120</sup> Anagnostopoulos et al. <sup>122</sup>
Isotype transformation	Light chain escape, development of hyposecretory disease	Brioli et al. <sup>123</sup> Ahn et al. <sup>124</sup>
High LDH levels at relapse		Dimopoulos et al. <sup>18</sup> Sellner et al. <sup>120</sup>

### Characteristics of prior or ongoing therapy

A thorough review of previous and ongoing therapies, duration of prior therapies, and both depth and DOR to prior treatment is necessary at the time of disease progression. Short DOR and progression while on therapy are associated with adverse outcomes.<sup>17,18</sup> Previous treatment-related toxicities are reviewed and attributed when possible to a specific agent.

### Transplant status

Potential eligibility for ASCT or allogeneic SCT (Allo-SCT) is an important consideration. A patient who has previously undergone single ASCT may be eligible for a second course of high-dose therapy with autologous stem cell rescue if the PFS after the first was at least 18–24 months. If the patient did not receive consolidation/maintenance therapy post initial ASCT, such therapy should be considered following the second ASCT. It should be also recognized that this target progression-free interval of at least 18 months post-ASCT was established before consolidation/maintenance was as widely practiced as is now the case. Allo-SCT is associated with significant treatment-related morbidity and mortality, but can be considered in appropriately selected younger patients with a suitable donor.

### Patient characteristics

Important clinical features such as performance status, co-morbidities and goals of care have a significant influence on MM treatment decisions, with less intensive approaches reserved for those with frailty and/or significant co-morbidities.

## GENERAL TREATMENT PRINCIPLES IN THE MANAGEMENT OF RELAPSED MM

### When to treat?

Treatment is indicated when patients develop symptomatic relapse, a rapidly rising paraprotein level or extramedullary disease. Patients experiencing biological relapse alone do not necessarily need to be treated immediately. In this case, the speed of increase of the monoclonal peak, such as a doubling time of 3 months or shorter, would suggest initiating treatment. For asymptomatic biochemical relapse and a slow rise in the paraprotein level, restaging with a stringent wait and watch approach and follow up at least every 3 months can be recommended. Some patients develop oligoclonal reconstitution post-ASCT, which can occur in up to 37% of patients in this setting.<sup>19</sup> This is transient, can be observed and should not be treated.

### General management

A patient who is naïve to an agent (or a class of drugs) is typically treated with a regimen incorporating this agent (or any agent from the drug class). A patient with relapsed MM who has not previously undergone ASCT, for example, can be considered for high-dose therapy. A patient who previously responded to a particular agent with a DOR of at least 6–9 months can be retreated at relapse with similar drugs used previously or in combination with other agents.<sup>20,21</sup>

Duration of therapy in relapsed MM is determined by the clinical context. Since no prospective studies addressing this issue are available, the following considerations are based on clinical experience only. The patient with aggressive disease characteristics at the time of relapse is likely to progress without ongoing therapy and typically requires continuous therapy. In the patient with indolent disease who responds to treatment, options include consolidation with ASCT, maintenance therapy or careful observation for a period of time without therapy, but caution here is warranted given the propensity of disease to sometimes rapidly evolve into a more aggressive phenotype.

### Approach to the patient with aggressive disease characteristics

Patients with high-risk disease without co-morbidities and with adequate performance status are generally treated with highly active three- or four-drug combinations to achieve maximal response. Appropriately selected patients who respond to initial therapy in the relapsed setting can then be considered for ASCT. Allo-SCT represents an option for a subset of treatment-responsive patients with younger age, an available human leukocyte antigen-matched donor, chemotherapy-sensitive disease and excellent performance status.

### Approach to the patient with indolent disease characteristics

Patients with indolent disease at relapse are generally treated with regimens that include an agent to which the patient is either naïve or has known sensitivity. It remains uncertain whether one- or two-drug regimens should be preferentially utilized in this setting over three- or four-drug regimens, although randomized trials increasingly support the three-drug approach for relapsed MM in general. Treatment intensification with ASCT can be considered for patients without prior exposure to high-dose therapy and those who sustained a prolonged response to prior autologous transplant.

## CURRENT TREATMENT REGIMENS IN RELAPSED AND REFRACTORY MM

With the development of multiple new therapeutic agents over the past decade, the repertoire of treatment options for relapsed MM has expanded considerably.

### Immunomodulatory drugs

*Thalidomide monotherapy.* In the initial phase II trial with single-agent thalidomide, 84 individuals with relapsed and refractory MM received daily thalidomide at doses ranging from 200 to 800 mg.<sup>22</sup> The overall response rate (ORR) was 32%, with 2-year event-free survival and overall survival (OS) rates of 20 and 48%, respectively.<sup>23</sup> The ORR to single-agent thalidomide in relapsed MM has ranged from 14 to 43% with median response durations of 12–14 months.<sup>23–29</sup>

Important toxicities associated with these high doses of thalidomide include thrombosis, sedation, fatigue and constipation.<sup>30,31</sup> Peripheral neuropathy (PN) is cumulative, being both dose and time dependent and can be irreversible.

*Thalidomide plus dexamethasone.* In an analysis of 12 phase II trials of 451 patients with relapsed or relapsed/refractory MM (RR MM) treated with thalidomide dexamethasone, the ORR was 46%.<sup>32</sup> Venous thromboembolism occurred in up to 25% of patients with relapsed MM receiving thalidomide with dexamethasone and/or chemotherapy, underscoring the need for effective thromboprophylaxis.<sup>33</sup>

*Lenalidomide monotherapy.* In a randomized phase II study, 70 patients with relapsed or relapsed/refractory disease were randomized to lenalidomide 30 mg daily or 15 mg twice daily for 21 days of every 28-day cycle.<sup>34</sup> The 15 mg twice daily dose was associated with increased grade 3/4 myelosuppression compared with daily dosing. The ORR to lenalidomide monotherapy was 25% with a median OS of 28 and 27 months in the 30 mg once daily and 15 mg twice daily groups. In a subsequent phase II study of single-agent lenalidomide involving 222 patients with RR MM, the rate of  $\geq$  partial response (PR) was 26%.<sup>35</sup> The median PFS and OS in this study were encouraging, at 4.9 and 23.2 months, respectively.

**Lenalidomide plus dexamethasone.** The efficacy of lenalidomide plus dexamethasone was demonstrated in two randomized, double-blind, placebo-controlled studies in patients with RR MM—the MM-009 trial and the MM-010 trials (Table 2).<sup>36,37</sup> In both studies, patients were randomized to lenalidomide 25 mg or placebo on days 1–21 of a 28-day cycle. All patients received dexamethasone on days 1–4, 9–12 and 17–20 for four cycles and on days 1–4 only in subsequent cycles. Lenalidomide plus dexamethasone (dex) produced superior PR or better rates (Table 1) (MM-009: 61%; MM-010: 60.2%) compared with placebo-dex (MM-009: 19.9%; MM-010: 24%), and the median time to progression (TTP) was significantly longer with lenalidomide plus dex (MM-009: 11.1 months; MM-010: 11.3 months) compared with placebo-dex (4.7 months in both trials). Grade 3/4 toxicities associated with the combination included anemia, neutropenia, thrombocytopenia and venous thromboembolism.<sup>33</sup> These pivotal studies led to the approval of lenalidomide plus dex for the treatment of RR MM.

**Pomalidomide monotherapy.** Pomalidomide, which was approved by the Food and Drug Administration in February 2013, and in combination with dexamethasone by the European Medicines Agency in August 2013, was evaluated as monotherapy at doses ranging from 1 to 10 mg in a phase I study involving 24 patients.<sup>38</sup> The rate of  $\geq$ PR was 50%, and rate of  $\geq$ MR 67%. With further evaluation the single-agent activity of pomalidomide in patients with disease resistant to bortezomib and lenalidomide is around 15%.<sup>39</sup>

Pomalidomide is currently indicated in patients who have received at least 2 prior therapies (including lenalidomide and bortezomib) and have disease progression on or within 60 days of completion of the last therapy.

**Pomalidomide plus dexamethasone.** In the pivotal 002 randomized Phase 2 study of pomalidomide with or without dexamethasone confirmed ORR of the order of 34% (pomalidomide with dexamethasone) in RR MM in patients resistant to both immunomodulatory drugs (IMiDs) and proteasome inhibitors, including bortezomib and carfilzomib, as well as showing activity in patients with high-risk features including adverse cytogenetics.<sup>39</sup> Pomalidomide plus low-dose dexamethasone was compared with high-dose dexamethasone in an open-label phase III study involving 302 patients, and demonstrated the superiority of the combination in terms of PFS (4.0 vs 1.9 months,  $P < 0.0001$ ) and OS (12.7 vs 8.1 months,  $P = 0.028$ ).<sup>40</sup> Interestingly, patients with del17p responded better to a combination of pomalidomide and dexamethasone compared to patients with a translocation t(4;14) in a recent French study.<sup>41</sup>

## Proteasome Inhibitors

**Bortezomib monotherapy.** In a pivotal phase II study, bortezomib monotherapy administered to 202 patients with RR MM was associated with an ORR of 34%.<sup>42</sup> The median DOR was 12 months, and median OS, 16 months. The phase III APEX study confirmed the efficacy of single-agent bortezomib in RR MM (Table 3).<sup>43</sup> The study included 669 patients with a median of two prior therapies with RR MM who were randomized to intravenous (i.v.) bortezomib or high-dose dex. Bortezomib was superior in terms of ORR (46 vs 21%,  $P < 0.001$ ), median TTP (6.2 vs 3.5 months,  $P < 0.001$ ) and 1-year OS rate (80 vs 66%,  $P < 0.003$ ). Bortezomib activity was independent of chromosomal abnormalities such as del(13) and t(4;14).<sup>44</sup> Bortezomib-related toxicities include PN, gastrointestinal symptoms, fatigue, thrombocytopenia, neutropenia and herpes zoster reactivation.

**Subcutaneous versus intravenous bortezomib.** A phase III study compared the efficacy and safety of subcutaneous (s.c.) versus i.v. bortezomib in patients with relapsed/refractory MM. S.c. bortezomib demonstrated non-inferior efficacy in comparison with standard i.v. administration, with an improved safety profile, especially decreased neurotoxicity.<sup>45</sup>

**Bortezomib plus dexamethasone.** The addition of dexamethasone to i.v. bortezomib improves rates of response and also improves tolerability.<sup>46,47</sup> The combination of bortezomib with dexamethasone administered as a second-line therapy was associated with  $\geq$ PR in 66% of patients, with a median TTP of 9.5 months.<sup>48</sup>

**Carfilzomib.** Carfilzomib (formerly PR-171) is an irreversible proteasome inhibitor.<sup>49</sup> Two parallel phase 2 studies, PX-171-003-A1<sup>50</sup> and PX-171-004,<sup>51</sup> evaluated carfilzomib in patients with RR MM (Table 3).

In the open-label, single-arm phase II PX-171-003-A1 study, patients received carfilzomib 20 mg/m<sup>2</sup> i.v. twice weekly for 3 out of 4 weeks in cycle 1, then 27 mg/m<sup>2</sup> for up to 12 cycles with low-dose dexamethasone as premedication. Patients had a median of 5 prior lines of therapy and 80% were refractory to or intolerant of both bortezomib and lenalidomide. ORR was 23% with median DOR of 7.8 months and a median OS of 15.6 months. Common adverse events included fatigue (49%), anemia (46%), nausea (45%) and thrombocytopenia (39%). Twelve percent experienced PN, primarily grades 1 to 2, with some significant cardiopulmonary toxicity as well as renal dysfunction also encountered.<sup>50</sup>

In the PX-171-004 study, carfilzomib with low-dose dexamethasone premedication was given to bortezomib-naïve RR MM patients. Patients in cohort 1 received i.v. carfilzomib 20 mg/m<sup>2</sup> for all treatment cycles, while those in cohort 2 received 20 mg/m<sup>2</sup>

**Table 2.** Pivotal clinical trials evaluating lenalidomide-containing regimens in relapsed and/or relapsed-refractory MM

Regimen	Phase	N	ORR %	>PR %	>VGPR %	CR/nCR %	TTP mos	PFS mos	OS mos
Len-dex vs dex <sup>37</sup>	III	177		61		14.1	11.1		29.6
		176		19.9		0.6	4.7		20.2
Len-dex vs dex <sup>36</sup>	III	176		60.2		15.9	11.3		Not reached
		175		24.0		3.4	4.7		20.6
Lenalidomide, bortezomib, dexamethasone <sup>77</sup>	II	64	78	64		25	9.5	9.5	26
		31		81	7	29		Not reached	Not reached
Bendamustine, Len, Dex <sup>64,71</sup>	I/II	36		52	24	0		2-year PFS 56%	30 months—80% OS at
		18		92	23	15 (nCR)	4.4	NA	Not reached
Carfilzomib, Len, Dex <sup>126</sup>	Ib	32		55	20	10		NA	NA

Abbreviations: Dex, dexamethasone; Len, lenalidomide; mos, months; NA, not available; OS, overall survival; PFS, progression-free survival; Thal, thalidomide; TTP, time to progression.

**Table 3.** Pivotal clinical trials evaluating proteasome inhibitor-containing regimens in relapsed and/or relapsed-refractory MM

Regimen	Phase	N	ORR %	>PR %	>VGPR %	CR/nCR %	TTP mos	PFS mos	OS mos
Btz +/- Dex <sup>42</sup>	II	202	34	27		10	7		16
Btz 1.0 (+/- dex)	II	28	33 (44)	30 (37)		11 (19)	7		26.7
Btz 1.3(+/- dex) <sup>127</sup>		26	50 (62)	38 (50)		4 (4)	11		60
Btz	III	333	46	38		13	6.2		29.8
Dex <sup>43</sup>		336	35	18		2	3.5		23.7
Btz s.c.	III	148	42			20	10.4	10.2	1-y 73%
Btz i.v. <sup>45</sup>		74	42			22	9.4	8	1-y 77%
Btz + PLD	III	324	44		27	13	9.3	9.3	15-mo 76%
Btz <sup>74</sup>		322	41		19	10	6.5	6.5	15-mo 65%
VTD	III	135	93	86	61	45	19.5	18.3	2-y 71%
TD <sup>75</sup>		134	83	74	38	21	13.8	13.6	2-y 65%
Btz +Cycl+Pre <sup>69</sup>	I-II	37	95	88	61	50		1-y 83%	1-y 100%
Btz + Adria + Dex <sup>73</sup>	II	64		67	25			1-y 34%	1-y 66%
Bendamustine + Btz + Dex <sup>71</sup>	II	83	75	67	28	12		67% at 6 mo	6-mo 80%
Btz +HDAC inh	III	637	56					7.6	
Btz+ Dex <sup>128</sup>			41					6.8	
Carfilzomib <sup>50</sup>	II	257	23.7						15.6
Carfilzomib Btz naïve	II	129	42.4				8.3		
20 mg/m <sup>2</sup>			52.2				Not reached		
20/27 mg/m <sup>2</sup> <sup>51</sup>									

Abbreviations: Adria, adriamycin; Btz, bortezomib; Cycl, cyclophosphamide; Dex, dexamethasone; HDAC inh, histone deacetylase inhibitor; i.v., intravenous; mos, months; PLD, pegylated liposomal doxorubicin; Pre, prednisone; s.c., subcutaneous; TD, thalidomide dexamethasone; VTD, velcade thalidomide dexamethasone.

in cycle 1 and 27 mg/m<sup>2</sup> in subsequent cycles. The ORR was 59 and 64% in cohorts 1 and 2, respectively. Median DOR was 13 months and not reached in the respective cohorts, and median TTP was 8 months and not reached, respectively.<sup>51</sup>

Carfilzomib is indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of last therapy, and was recently approved for relapsed disease in combination with lenalidomide and dexamethasone.

#### Bendamustine

**Bendamustine monotherapy.** Bendamustine has activity as a single agent. In a dose-escalation study of bendamustine in 31 patients up to the age of 70 years (60 up to 100 mg/m<sup>2</sup>) the ORR was 55% with a PFS of 8 months.<sup>52</sup>

**Bendamustine plus prednisone.** A retrospective study analyzed the use of bendamustine in 110 patients with RR MM after prior therapy with alkylators, steroids, IMiDs (lenalidomide or thalidomide) and bortezomib. Bendamustine was given at the doses of 60 to 150 mg/m<sup>2</sup> on days 1 and 2 in combination with prednisone in 28 days cycles. The OR rate was 30% (2% CR+28% PR). The median PFS was 9.3 months with a median OS of 12.4 months.<sup>53</sup>

#### Panobinostat

Panobinostat is a potent oral pan-deacetylase inhibitor that in preclinical studies has synergistic antimyeloma activity when combined with bortezomib and dexamethasone.<sup>54</sup> A phase 3 trial, PANORAMA1, included 768 patients with relapsed or RR MM who were randomly assigned to receive 21 day cycles of placebo or panobinostat (20 mg; on days 1, 3, 5, 8, 10, 12, orally), both in combination with bortezomib (1.3 mg/m<sup>2</sup>) on days 1, 4, 8, 11 i.v.) and dexamethasone (20 mg on days 1, 2, 4, 5, 8, 9, 11, 12 orally). Median PFS was significantly longer in the panobinostat group than in the placebo group (11.99 vs 8.08 months; hazard ratio (HR)=0.63; P<0.0001). Median OS was 33.64 months for the panobinostat group and 30.39 months for the placebo group (HR 0.87, P=0.26). The proportion of patients achieving an ORR did not differ between treatment groups; however, the proportion of

patients with a complete response (CR) or complete response (nCR) was significantly higher in the panobinostat group than in the placebo group (27.6 vs 15.7%; P=0.00006). Thrombocytopenia, diarrhea and fatigue were more frequent in the panobinostat group. Panobinostat is approved for the treatment of relapsed and refractory multiple myeloma after bortezomib and lenalidomide failure.<sup>55</sup>

#### Multidrug combinations

##### IMiD plus alkylating agents

**Melphalan plus thalidomide:** In a phase II study, patients with relapsed MM received 100 mg/day thalidomide escalated weekly up to 600 mg/day alone (n=23) or in combination with oral 0.20 mg/kg/day melphalan administered monthly for four consecutive days (n=27).<sup>56</sup> A PR was observed in 59% of melphalan plus thalidomide-treated patients compared with 26% in the thalidomide group (P=0.009). A CR was achieved by three patients treated with melphalan plus thalidomide versus none in the thalidomide monotherapy group. With 13 months median follow-up (range 6–32), PFS at 2 years was significantly longer in the combination group (61 vs 45%; P=0.0376), whereas OS did not differ significantly.

**Cyclophosphamide, thalidomide, dexamethasone:** In a phase II trial of weekly oral cyclophosphamide 300 mg/m<sup>2</sup>, monthly pulsed low-dose dexamethasone and thalidomide 300 mg/day, the PR rate was 62%, including 17% CR. Twenty-seven percent of patients developed infection, most of which were respiratory, but there were no infection-related deaths.<sup>57</sup>

In another phase II study evaluating the cyclophosphamide, thalidomide, dexamethasone combination, 53 patients received pulsed cyclophosphamide (150 mg/m<sup>2</sup> twice daily, days 1–5), thalidomide (400 mg, days 1–5 and 14–18) and dexamethasone (20 mg/m<sup>2</sup>, days 1–5 and 14–18). Thirty-two patients (60%) achieved PR with a median time to response of 1.5 months.<sup>58</sup>

**Lenalidomide, cyclophosphamide, dexamethasone:** The combination of cyclophosphamide, lenalidomide and dexamethasone was evaluated in a phase I/II study in which 31 patients with a median of 3 prior lines of therapy received oral cyclophosphamide (dose range 300–700 mg) on days 1 and 8 of a 28-day cycle; lenalidomide 25 mg on days 1–21; and dex on 20 mg days 1–4

and 8–11 (Table 2).<sup>59</sup> The rate of  $\geq$  PR was 81%, with a CR rate of 29%. Among 10 patients treated at the maximum tolerated dose of cyclophosphamide 600 mg, the CR rate was 40%.<sup>60</sup> High-grade toxicities included neutropenia, thrombocytopenia, infection and somnolence.

**Lenalidomide, cyclophosphamide, prednisone:** The combination of lenalidomide and continuous oral cyclophosphamide and prednisone was evaluated in a small series of heavily pretreated and lenalidomide refractory patients. Response to therapy was seen in 50% of patients, including 14.3% of patients with a CR and 21.4% with a very good partial response (VGPR).<sup>61</sup> This study was followed by an open-label phase I/II study that evaluated the optimal dose of the different drugs. The maximum tolerated dose was lenalidomide 25 mg (d1–d21), continuous cyclophosphamide (50 mg/day) and prednisone 20 mg/day. The ORR was 67% with a PFS of 6.3 months and OS of 15.5 months.<sup>62</sup> Grade 3 hematologic adverse events included neutropenia (22%), thrombocytopenia (19%) and anemia (12%). Grade 3 non-hematologic adverse events included infections (22%) and cardiac complications (10%).

**Lenalidomide, melphalan, prednisone, thalidomide:** In a phase II study involving 44 patients with RR MM and maximum two prior lines of therapy, lenalidomide (10 mg/day) was administered on days 1–21 in combination with thalidomide 50 or 100 mg/day, oral melphalan (0.18 mg/kg) and oral prednisone (2 mg/kg) on days 1–4 of each 28-day cycle. Six cycles of therapy were followed by lenalidomide maintenance until unacceptable toxicity or progression. Seventy-five percent achieved  $\geq$  PR, including 32% VGPR and 2% CR. The 1-year PFS was 51% and 1-year OS was 72%. Grade 4 hematologic adverse events included neutropenia (18%), thrombocytopenia (7%) and anemia (2%). Grade 3 non-hematologic adverse events included infections (14%), neurologic toxicity (4.5%) and fatigue (7%).<sup>63</sup>

**Lenalidomide, bendamustine, dexamethasone:** In a phase I/II study involving 29 patients with RR MM, lenalidomide plus bendamustine and dexamethasone yielded a PR rate of 52% and VGPR 24%.<sup>64</sup> The median PFS was 6.1 months, the 1-year PFS 20% and the 1-year OS 93%. Frequent toxicities included neutropenia, thrombocytopenia, anemia and fatigue.

A similar combination with prednisone instead of dexamethasone and lower doses of bendamustine (60–75 mg/m<sup>2</sup>) gave encouraging results: 76% ORR (5% CR+71% PR) and at 18 months 48% PFS and 64% OS.<sup>65</sup>

**Pomalidomide, cyclophosphamide, dexamethasone:** Pomalidomide, cyclophosphamide and dexamethasone was compared with pomalidomide and dexamethasone in a randomized phase II trial involving patients with RR MM who were lenalidomide refractory and received at least two prior therapies.<sup>66</sup> Patients received pomalidomide 4 mg days 1–21 plus weekly dexamethasone 40 mg in a 28-day cycle, with or without oral cyclophosphamide 400 mg days 1, 8 and 15. The rate of PR or better was 39% versus 65% ( $P=0.03$ ) in the pomalidomide-dex and pomalidomide-cyclophosphamide-dex arms, respectively. PFS was superior with pomalidomide-cyclophosphamide-dex (9.2 versus 4.4 month,  $P=0.04$ ) and there was a trend toward improvement in OS (16.4 versus 10.5 months,  $P=0.08$ ).

#### *IMiD plus anthracyclines*

**Thalidomide, liposomal doxorubicin, dexamethasone:** The combination of thalidomide, liposomal doxorubicin and dexamethasone was evaluated in a phase II involving 50 patients with RR MM who received pegylated liposomal doxorubicin 40 mg/m<sup>2</sup> on day 1 of a 28-day cycle, oral dexamethasone 40 mg days 1–4 and 9–12 and thalidomide 100 mg daily. The ORR was 76%, with 26% achieving a CR. The median event-free survival was 17 months

and median OS was not reached. Grade 3 non-hematologic toxicity occurred in 12% of patients, thromboembolic disease in 12% and severe infection in 16%.<sup>67</sup>

**Lenalidomide, adriamycin and dexamethasone:** In a phase I/II trial, the combination of lenalidomide, adriamycin, and dexamethasone was evaluated in 69 patients with RR MM and yielded an ORR of 73%.<sup>68</sup> Frequent grade 3/4 toxicities included neutropenia, thrombocytopenia and infection.

#### *Proteasome inhibitors plus alkylating agents*

**Bortezomib, oral cyclophosphamide, prednisone:** The combination of i.v. bortezomib, weekly oral cyclophosphamide and alternate day prednisone was investigated in a phase I–II study (Table 2). The combination was highly active, and at the highest dose level of bortezomib 1.5 mg/m<sup>2</sup> days 1, 8 and 15; cyclophosphamide 300 mg/m<sup>2</sup> days 1, 8 and 15; and prednisone every other day, the ORR was 95% with an encouraging 83% 1-year PFS and 100% 1-year OS.<sup>69</sup> Other versions of this regimen include cyclophosphamide i.v. 300–500 mg/m<sup>2</sup> (days 1, 8, 15), bortezomib 1.3 mg/m<sup>2</sup> (days 1, 4, 8, 11) and dexamethasone (days 1, 2, 4, 5, 8, 9, 11, 12) every 21 days.

**Bortezomib, bendamustine, dexamethasone:** Three phase II studies were reported, all of them with bendamustine at the doses of 70 mg/m<sup>2</sup> on days 1 and 8 (or 4) every 28 days. The first one reported 77% OR rate (20% CR+57% PR) with a median PFS of 15.5 months.<sup>70</sup> The second one focused on patient in first relapse. The response rates were similar with 70% OR rate but survival was slightly shorter: median PFS of 10.8 months and an OS of 23 months.<sup>71</sup> In the third study, the survival was very comparable (PFS of 9.7 months and OS of 25.6 months) and patients with adverse cytogenetics (defined by *in situ* hybridization) had similar results.<sup>72</sup> In all three studies, the toxicity was mostly hematological and generally limited.

#### *Proteasome inhibitors plus anthracyclines*

**Bortezomib, doxorubicin, dexamethasone:** The combination of bortezomib, doxorubicin, and dexamethasone was evaluated in 64 patients with relapsed MM (Table 2).<sup>73</sup> Prior treatments among these patients included ASCT (58%), anthracycline (70%) and/or bortezomib (27%). PR or better was achieved in 67% of this heavily pretreated population and VGPR in 25%. Common grades 3 or 4 toxicities included thrombocytopenia, neutropenia, anemia and PN.

**Bortezomib plus pegylated liposomal doxorubicin:** A large-scale randomized phase III trial comparing bortezomib alone (1.3 mg/m<sup>2</sup> i.v.) with bortezomib+pegylated liposomal doxorubicin (30 mg/m<sup>2</sup>) showed superiority of the combination in terms of median TTP (9.3 vs 6.5 months,  $P < 0.001$ ) and OS rate (76 vs 65%,  $P=0.03$ ) although the increase in ORR was only modest (44 vs 41%,  $P=0.43$ ) (Table 2).<sup>74</sup> These important results led to regulatory approval of bortezomib plus pegylated liposomal doxorubicin in 2007.

#### *IMiD plus proteasome inhibitors*

**Bortezomib, thalidomide and dexamethasone:** A prospective, multicenter, phase III trial (MMVAR/IFM 2005-04 trial) compared the efficacy and safety of bortezomib plus thalidomide and dex with thalidomide and dex in 269 patients who relapsed after ASCT (Table 2).<sup>75</sup> Median TTP was longer with bortezomib (1.3 mg/m<sup>2</sup>) plus thalidomide (200 mg/day) and dex (40 mg/day d1–d4) (19.5 vs 13.8 months,  $P=0.001$ ), CR plus nCR was higher (45 vs 25%,  $P=0.001$ ) and median DOR was longer (17.2 vs 13.4 months,  $P=0.03$ ). Two-year OS favored the three-drug combination (71 vs 65%,  $P=0.093$ ). Grade 3 PN was more frequent with the

three-drug combination (29 vs 12%,  $P=0.001$ ) as were the rates of grades 3 and 4 infection and thrombocytopenia.

**Lenalidomide plus bortezomib:** In a phase I study evaluating lenalidomide and bortezomib in RR MM, the ORR was 61%, with a CR/nCR rate of 8%.<sup>76</sup> The most common grades 3 or 4 treatment-related toxicities were neutropenia, thrombocytopenia, anemia and leukopenia; there were no cases of grade 3/4 PN. Grades 1 or 2 PN occurred in 42% of patients and was manageable. Median OS was encouragingly at 37 months. In a subsequent phase II study of bortezomib plus lenalidomide with added dexamethasone in RR MM, the ORR was 78% and grades 3/4 toxicities included 30% neutropenia, 22% thrombocytopenia and only 3% PN (Table 1).<sup>77</sup> Median TTP was 9.5 months, median PFS was 9.5 months and the 2-year OS rate was 55%.

**Carfilzomib, lenalidomide and dexamethasone:** Carfilzomib, lenalidomide and low-dose dexamethasone has shown activity in a phase II study of 52 patients with RR MM.<sup>78</sup> It was confirmed in a phase III trial in which 792 patients were randomly assigned to carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group).<sup>79</sup> PFS, the primary end point, was significantly improved with carfilzomib (median, 26.3 vs 17.6 months (HR=0.69;  $P=0.0001$ )). The median OS was not reached in either group at the interim analysis. The ORR were 87.1 and 66.7% in the carfilzomib and control groups, respectively ( $P < 0.001$ ); 31.8 and 9.3% of patients in the respective groups had a  $\geq$ CR; 14.1 and 4.3% had a stringent CR). Encouragingly, patients in the carfilzomib group also reported superior health-related quality of life.

Adverse events of grade 3 or higher were reported in 83.7 and 80.7% of patients in the carfilzomib and control groups, respectively, with similar rates of treatment discontinuation between the arms, although rates of hypertension and venous thrombosis were higher in the carfilzomib group.

**Carfilzomib, pomalidomide and dexamethasone:** The combination of carfilzomib, pomalidomide and dexamethasone has been evaluated in a phase I/II study.<sup>80</sup> The phase I portion of the study established maximum tolerated dose at carfilzomib 27 mg/m<sup>2</sup> days 1, 2, 8, 9, 15 and 16 of a 28-day cycle; pomalidomide 4 mg days 1–21; and dexamethasone 40 mg days 1, 8, 15 and 22. In an interim analysis including data from 67 patients, the ORR was 64%, with a rate of  $\geq$ MR of 81%. Median PFS and OS were 12.0 and 16.3 months, respectively. Grade  $>3$  adverse events included fatigue, neutropenia, anemia, thrombocytopenia and diarrhea.

#### *IMiD-proteasome inhibitor plus alkylating agents*

**Bortezomib, cyclophosphamide, thalidomide, dex:** The clinical efficacy and safety of this four-drug combination was assessed in 70 patients with RR MM.<sup>81</sup> They received at least two cycles of bortezomib (1.3 mg/m<sup>2</sup> i.v. days 1, 4, 8 and 11), cyclophosphamide (150 mg/m<sup>2</sup> orally days 1–4), thalidomide (50 mg/day daily) and dexamethasone (20 mg/m<sup>2</sup> i.v. days 1, 4, 8 and 11). The ORR was very encouraging at 88%, with 46% CR, 9% VGPR and 33% PR. After a median follow-up of 12.6 months, median PFS was 14.6 months with a 3-year PFS of 14%. Median OS was 31.6 months with a 3-year OS of 47%. Grades 3 or 4 toxicities included thrombocytopenia (12%), neutropenia (4%), peripheral neuropathy (3%) and very rare cases of thrombosis ( $< 1\%$ ).

#### *IMiD-alkylating agent-cisplatin-etoposide, with or without proteasome inhibitors*

**Dexamethasone and thalidomide plus cisplatin, doxorubicin, cyclophosphamide, etoposide (DT-PACE):** DT-PACE is a salvage therapy which combines high-dose dexamethasone (40 mg orally

daily for 4 days) with thalidomide at 100 mg per day and a 4-day continuous infusion of cisplatin (10 mg/m<sup>2</sup>/day), doxorubicin (10 mg/m<sup>2</sup>/day), cyclophosphamide (400 mg/m<sup>2</sup>/day) and etoposide (40 mg/m<sup>2</sup>/day). The cycles are usually administered every 4–6 weeks and 2–4 cycles are planned.<sup>82</sup> This regimen is commonly used as last salvage treatment because it has drugs that have often not been used before, some of which penetrate the blood brain barrier. In a retrospective study, the role of DT-PACE as salvage therapy for high-risk patients with aggressive relapsed and refractory MM was analyzed. The ORR was 49% (VGPR = 16%, PR = 33%) with stable disease in 36%. The PFS was 5.5 months and the OS was 14 months. The toxicity was mostly hematological.<sup>83</sup>

**Bortezomib, dexamethasone and thalidomide (VDT-PACE):** Bortezomib in combination with DT-PACE has been evaluated in a series of 16 patients with RR MM in whom DT-PACE was administered as described previously along with i.v. bortezomib 1.0 mg/m<sup>2</sup> days 1, 4, 8 and 11.<sup>84</sup> The ORR was 63% and median PFS 7 months. Hematologic toxicity was common, including grade 3–4 neutropenia in 56% and febrile neutropenia in 56%.

### **AUTOLOGOUS STEM CELL TRANSPLANTATION**

A number of studies have examined outcomes of second ASCT for relapsed disease in patients who had undergone ASCT at an earlier point in their management. The Royal Marsden Group analyzed 172 patients who had relapsed after a first transplant, 68% of whom received cyclophosphamide-vincristine-doxorubicin-melphalan-prednisone as salvage chemotherapy while the others received a non-specified salvage approach.<sup>85</sup> Forty-eight of the patients subsequently received a second high-dose melphalan autograft based on suitability and patient choice, whereas 52% received a variety of other treatment approaches. There was no significant difference between these two groups in terms of event free survival (1.3 vs 0.9 years) or OS (2.9 vs 1.7 years). A relapse-free interval of over 18 months following first transplant was associated with a prolonged OS (2.9 vs 1.0 year) regardless of whether a second transplant was received although a trend toward superior OS for those receiving a second autograft was suggested (4.6 vs 2.9 years;  $P=0.33$ ).

Similar outcomes were reported in a second study that assessed outcomes of 41 patients who received a second melphalan-based autograft as part of salvage chemotherapy.<sup>86</sup> All had received preceding salvage chemotherapy but only 37% had chemosensitive disease at the time of second transplant. Although an ORR of 55% was reported following second autograft, this was associated with a treatment-related mortality of 7%. The median PFS after second autograft was 8.5 months and median OS was 20.7 months. Multivariate analysis of prognostic markers for PFS identified  $\geq 5$  prior lines of therapy and poor response to first autograft as poor prognostic markers. Similarly,  $\geq 5$  prior lines of therapy and TTP  $\leq 12$  months following first autograft were predictive for a poor OS.

Several studies have suggested that a minimum interval of 18 months with a range of 1.5–3 years from first ASCT to relapse results in a second PFS of about half that time after salvage ASCT, prompting many centers to view at least 18 months as a reasonable interval after first ASCT to recommend second ASCT in relapsed patients.

In order to consider salvage second ASCT, stem cells must have been collected prior to the first ASCT or a new collection has to be done. It has been shown that mobilization after reinduction using various mobilization regimen (granulocyte colony stimulating factor only, cyclophosphamide+granulocyte colony stimulating factor or plerixafor) is feasible.<sup>87</sup>

## ALLOGENEIC SCT

Allo-SCT is a possible option for treatment of relapse in patients younger than 65–70 years, as shown in recent studies of patients relapsing after ASCT.<sup>88–93</sup> Myeloablative conditioning has been considered associated with excessive non-relapse mortality as shown in earlier studies both as upfront treatment and for relapsed patients.<sup>94,95</sup> However reducing the intensity of the conditioning before allotransplantation (RICallo) should reduce non-relapse mortality.<sup>94,96</sup> In recent studies non-relapse mortality with RICallo has been in the range of 10–16% in patients treated upfront after ASCT and up to 26% in relapsed/progression patients usually heavily pretreated before RICallo. This has been considered a reasonable risk based on the observation that relapse risk is reduced and PFS improved. However, the impact on OS is controversial, not only in upfront treatment, but also in RR MM. In one retrospective study of 51 heavily pretreated relapsed and refractory patients the PFS and OS at 2 years were 19 and 32%, respectively.<sup>88</sup> Seven of these patients were in remission up to 6 years following RICallo. In a recently published prospective study, 169 progressive or relapsed patients following ASCT underwent human leukocyte antigen typing.<sup>89</sup> Out of 75 patients with a suitable donor, 68 underwent RIC allo, either with an identical sibling donor ( $n=24$ ) or an human leukocyte antigen-matched unrelated donor ( $n=44$ ). Patients who did not have a donor received novel agents including lenalidomide and bortezomib, at the discretion of the treating physician. The 2-year PFS from study entry was 42% in the RIC allo group, which was significantly better than 18% in the non-RIC donor group. However there was no significant difference in OS.

Allo-SCT is frequently used as a last option, when other approaches are no longer effective. Some patients may benefit from the treatment, but earlier use of this modality in the tandem ASCT/RICallo setting may be a better option although tolerability can be challenging.<sup>97,98</sup> Studies of RIC allo modalities are in progress both for treatment of patients with relapsed disease and for the upfront treatment of high-risk patients. Such studies should be compared with the best options using new drug combinations, like bortezomib plus thalidomide and dex which showed encouraging results in a recent prospective European Blood and Marrow Transplantation (EBMT) trial of patients relapsing after ASCT.<sup>75</sup> Such studies may help better define the role for allogeneic SCT in the treatment of RR MM.

### Specific management recommendations

#### First relapse

- Clinical trial participation should be offered if an appropriate study is available.
- In patients who experience a high quality, prolonged response with minimal toxicity to initial therapy, re-treatment can be considered if they have obtained at least a 6–9 months treatment-free interval. The alternative is to change to a different class of drug and reserve the original treatment scheme for second relapse.
- We recommend ASCT be considered for eligible patients who have not had an ASCT in first line, or had an ASCT with long response duration.
- We advise patients who experience suboptimal response or significant toxicity with initial therapy receive a regimen that incorporates at least one agent to which the patient has not been previously exposed.
- There is no specific preference between regimens that contain lenalidomide, bortezomib, or both drugs; the choice of regimen should be based on response and tolerability to immediate prior therapy, current clinical status and co-morbidities of the patient, and access and availability of agents.
- We suggest patients with poor prognosis disease characteristics at time of relapse be considered for three- or four-drug

regimens while those with indolent disease characteristics be considered for one- or two-drug combinations, recognizing that randomized studies are necessary to validate these recommendations.

- We recommend patients with poor prognosis disease characteristics be treated until disease progression recognizing the risk of rapid relapse in the absence of sustained exposure to chemotherapy. Treatment-free intervals can be considered in patients with indolent disease characteristics based on discretion of the treating physician and preferences of the patient.
- We recommend carfilzomib and pomalidomide be primarily used for patients refractory and/or intolerant to both bortezomib and lenalidomide.
- We recommend allogeneic stem cell transplantation be discussed in eligible patients with poor prognostic features, preferably in the context of a clinical trial.

#### Second relapse and beyond

- Clinical trial participation should be offered if an appropriate study is available.
- We recommend patients in second relapse or beyond receive a salvage regimen incorporating at least one agent to which there has not been prior evidence of resistance or intolerance.
- We suggest patients with aggressive disease characteristics at time of relapse be considered for three- or four-drug regimens while those with indolent disease characteristics be considered for one- or two-drug regimens, and here in cytotoxic agents can be added to appropriate proteasome inhibitor and IMiD-based combinations.
- We recommend patients in second relapse and beyond receive ongoing therapy until the particular regimen is no longer tolerated or there is evidence of disease progression, at which time an alternative regimen should be chosen.

Regimens that can be employed in first or subsequent stages of relapse are summarized in Table 4 with level of evidence and grade of recommendation (<http://www.cebm.net/?o=1025>) corresponding to each regimen. However, with increasing episodes of relapse, less information from randomized trials is available making evidence-based suggestions difficult. Hence, the suggestions made are based mainly on expert experience.

*Relapse and refractory to lenalidomide and bortezomib.* In 2011, a retrospective study conducted on behalf of the International Myeloma Working Group established that patients with relapsed MM, who were refractory to bortezomib and refractory to or ineligible to receive treatment with an IMiD (thalidomide or lenalidomide), had a OS and event-free survival of 9 and 5 months, respectively.<sup>16</sup> Treatment options in these patients are limited. Carfilzomib and pomalidomide, in conjunction with dexamethasone, have shown some efficacy in patients refractory to bortezomib and lenalidomide, respectively.

- We recommend a regimen containing carfilzomib or pomalidomide be considered for patients with myeloma relapsed and refractory to lenalidomide and bortezomib.
- Carfilzomib should preferably be used in combination with lenalidomide and low-dose dexamethasone consistent with the results of the ASPIRE trial.<sup>79</sup> Similarly, pomalidomide is preferably used in combination with low-dose dexamethasone, and can be combined with other agents, including bortezomib. Besides these regimens, there is no specific preference between other regimens that contain pomalidomide, carfilzomib or both drugs in this setting; the choice of regimen should be based on response and tolerability to immediate prior therapy, current



**Table 4.** Level of evidence for specific regimens used in the treatment of relapsed–refractory myeloma

Regimen	Level of evidence	Grade of recommendation
<i>One-drug regimens</i>		
Bortezomib	I	A
Carfilzomib	II	B
Thalidomide	II	B
Lenalidomide	II	B
<i>Two-drug regimens</i>		
Bortezomib plus dexamethasone	II	B
Bortezomib plus liposomal doxorubicin	I	A
Thalidomide plus dexamethasone	II	B
Lenalidomide plus dexamethasone	I	A
Pomalidomide plus dexamethasone	II	A
Lenalidomide plus bortezomib	II	B
<i>Three-drug regimens</i>		
Bortezomib–thalidomide–dexamethasone	I	A
Cyclophosphamide–bortezomib–prednisone	II	B
Cyclophosphamide–lenalidomide–dexamethasone	II	B
Cyclophosphamide–thalidomide–dexamethasone	II	B
Lenalidomide–bortezomib–dexamethasone	II	A
Bendamustine–bortezomib–dexamethasone	II	B
Bendamustine–lenalidomide–dexamethasone	II	B
Thalidomide–liposomal doxorubicin–dexamethasone	II	B
Carfilzomib–lenalidomide–dexamethasone	II	A
<i>Four-drug regimens</i>		
Cyclophosphamide–bortezomib–thalidomide–dexamethasone	II	B
Lenalidomide–melphalan–prednisone–thalidomide	II	B

clinical status and co-morbidities of the patient, as well as access and availability of agents.

- Panobinostat in combination with bortezomib and dexamethasone can be considered for patients with myeloma whom are relapsed and refractory to lenalidomide and bortezomib, or similar combinations.

*Relapse and autotransplantation*

- We recommend consideration of a second autograft for salvage in patients who have a minimum TTP of at least 18 months or more after first ASCT.
- In patients who have not undergone an ASCT at first response, we recommend consideration at the time of first relapse.

*Relapse and allogeneic transplantation*

- We recommend consideration of an Allo-SCT largely in the context of clinical trials, particularly focusing on high-risk patients.
- Considering lack of consistent data indicating superiority of Allo-SCT over tandem auto SCT and concerns for treatment-related mortality despite RIC as well as rates of graft-versus-host disease in studies so far, consideration of an Allo-SCT within or outside a clinical trial should be with appropriate informed consent of the patient outlining the risks of treatment-related mortality and graft-versus-host disease.

*New agents and future directions in relapsed myeloma.* Numerous novel compounds are undergoing evaluation in RR MM; this topic was the focus of a recent report from the International Myeloma Working Group.<sup>99</sup> Monoclonal antibody therapy targeting plasma cell antigens including CS1 glycoprotein, CD38 and CD138 is showing promising results. The anti-CS1 monoclonal antibody, elotuzumab,<sup>100</sup> the anti-CD38 antibodies, daratumumab<sup>101</sup> and SAR650984, and the CD138 conjugate BT062 comprised of the anti-CD138 chimerized MAb and the cytotoxic agent DM4<sup>102</sup> are examples of monoclonal antibodies currently being investigated, with elotuzumab in combination with lenalidomide and dexamethasone being particularly active and well tolerated. Daratumumab is especially potent and highly effective in relapsed and

**Table 5.** Monoclonal antibodies in development in multiple myeloma

Target	mAb	Stage of development
<i>Surface molecules</i>		
CS1/SLAMF7	Elotuzumab	Phase 2/3
CD38	Daratumumab	Phase 1/2/3
	SAR650984	Phase 1/2
	MOR202	Phase 1/2
CD74	Milatumzumab	Phase 1/2
CD40	Dacetuzumab	Phase 1
CD56	Lorvotuzumab mertansine	Phase 1
CD138	BT062	Phase 1
<i>Signaling molecules</i>		
IL-6	Siltuximab	Phase 3
RANKL	Denosumab	Phase 3
B-cell activating factor (BAFF)	Tabalumab	Phase 2/3
VEGF	Bevacizumab	Phase 2
DKK1	BHQ880	Phase 2

refractory myeloma, both as monotherapy and in combination. A summary of monoclonal antibodies in development in MM is shown in Table 5.

The pan-histone deacetylase inhibitors romidepsin,<sup>103</sup> as well as the HDAC6 specific inhibitor, ACY 1215,<sup>104</sup> have demonstrated significant anti-MM effect in preclinical studies, with the latter now undergoing evaluation in combination with lenalidomide, pomalidomide and bortezomib, in various settings, and promising activity as well as favorable tolerability has been seen. Prior studies with vorinostat have also shown promise but a large randomized trial in combination with bortezomib demonstrated response rate advantages with only limited, although statistically significant, PFS improvement.<sup>105,106</sup>

Following promising early-phase trials of the agent in relapsed and refractory MM,<sup>107,108</sup> perifosine, a small-molecule inhibitor of the phosphatidylinositol 3-kinase (PI3-K/AKT) pathway was assessed in a phase III study in combination with bortezomib and dexamethasone versus bortezomib/dexamethasone, but this trial had to be closed prematurely because of resource limitations, slow accrual and no substantial difference in outcome seen on an interim analysis, although safety was favorable. Other studies of small molecule inhibitors in this category are ongoing.

The kinesin spindle protein inhibitor, ARRY-520, the cyclin-dependent kinase (CDK) inhibitor, dinaciclib, the CRM1 inhibitor selinexor, and another monoclonal antibody targeting B-cell activating factor (BAFF), tabalumab are examples of next generation novel agents that have preliminarily shown encouraging activity with ongoing trials in RR MM.<sup>109–111</sup>

Finally, with continued improvement in prevention and treatment of graft versus host disease and treatment-related mortality using a variety of agents, the role of allogeneic stem cell transplant may be revisited in the future in selected high-risk patients with RR MM, as well as recent strong interest in other immuno-oncologic strategies, including checkpoint inhibitors, vaccines and CAR-T therapy.

**CONCLUSION**

The management of relapsed MM requires a systematic approach based on several characteristic features of the patient. Prior treatment, including degree and depth of response, as well as treatment-related toxicities is important determinants in choosing subsequent treatment options. Risk stratification at the time of relapse based on chromosomal abnormalities and gene expression profiling is an emerging field. While OS of patients with MM has improved, the survival of patients progressing after treatment with the IMiDs and bortezomib remains dismal<sup>16</sup> underscoring the importance of continued efforts to better understand disease biology at the time of relapse and translate

this into viable and effective treatment options and rational combinations to further improve patient outcome.<sup>112–114</sup> The regulatory approval of multiple novel agents for relapsed and RR MM in 2015—panobinostat in combination with bortezomib and dexamethasone, pomalidomide plus dexamethasone, carfilzomib in combination with lenalidomide and dexamethasone, and most recently daratumumab (as the first monoclonal antibody), followed by elotuzumab in combination with lenalidomide and dexamethasone, and the oral proteasome inhibitor ixazomib in combination with lenalidomide and dexamethasone—represent a record for approvals in one year. These therefore are critical steps toward this goal and reflect real hope for the future in this otherwise incurable disease.

## CONFLICT OF INTEREST

JL reports grants from Novartis, grants from Celgene, grants from Onyx, grants from Millennium, outside the submitted work. LG reports personal fees from BMS, personal fees from Amgen, outside the submitted work. AM has received honorarium from Millennium Pharmaceuticals in the last 36 months for advisory board. GG reports grants and personal fees from Celgene, personal fees from Fujimoto Pharmaceutical Company, Japan, outside the submitted work. OS reports personal fees from Amgen, personal fees from Celgene and personal fees from Janssen. PV reports personal fees and other from Celgene Corporation, personal fees from Millennium Pharmaceuticals: A Takeda Oncology Company, personal fees from Novartis, other from Array Biopharma, grants and other from Oncopeptides, grants from Onyx Pharmaceuticals, grants and personal fees from GlaxoSmithKline, grants from Janssen and grants from Acetylon Pharmaceuticals. XL has received honorarium from Celgene, Millennium, Amgen, Janssen, Novartis, BMS, TEVA, LeoPHARMA and Pierre Fabre. MS has received Speakers Fees from Celgene and Janssen. HL reports grants from Takeda, grants and personal fees from Celgene, personal fees from Amgen/Onyx, personal fees from Janssen-Cilag. U-HM reports honoraria from Novartis, Mundipharma, Celgene, Amgen and Janssen and participated in advisory boards for Amgen and Celgene. WJC has received Honorarium from Celgene, Janssen, Millennium Takeda, Novartis and Onyx. EZ has received honoraria from Celgene and Janssen. CSC has received honorarium from Celgene and Janssen. TR has received honoraria from Celgene and Janssen. DJ has served on the advisory boards for Celgene, Onyx and Janssen; DJ has received payment for services from Celgene and Janssen. MR reports grants and personal fees from Celgene, grants from Janssen and grants from Onyx. POG has received honoraria from Celgene, Janssen and Takeda. ET has received honoraria and research grants from Amgen and Janssen-Cilag; ET has received honoraria from Celgene and Roche. PM has received compensation/honoraria for participation in scientific advisory boards for Celgene, Janssen, Sanofi, Karyopharm, The Binding Site and Bristol Myers Squibb. MD has received honoraria from Celgene, Janssen, Onyx, Takeda and Novartis. PM has served on the advisory board for Janssen, Celgene, Takeda, Novartis and Amgen. RO has been funded by the NIH, and has also received research grants from Array Biopharma, Bristol-Myers Squibb, Celgene Corporation, Janssen, Millennium Pharmaceuticals and Spectrum Pharmaceuticals. In addition, he has served on scientific advisory boards with compensation for Abbott Laboratories, Amgen, Inc., Array Biopharma, Bristol-Myers Squibb, Celgene Corporation, Forma Therapeutics, Incyte, Janssen, Millennium Pharmaceuticals, on scientific advisory boards without compensation for Acetylon Pharmaceuticals, Inc. KCA has served on Advisory boards for Celgene, Millennium, Sanofi Aventis, Gilead and Bristol-Myers Squibb. KA is also the scientific founder of Acetylon and Oncopep. AP has received honoraria from Janssen, Celgene, Amgen, Millennium/Takeda and BMS. SK's institution has received consulting fees from Merck, Millennium, Celgene, Sanofi/Genzyme and Onyx and grants from R01. SK has received payment for services from Sharp Healthcare. PGR has served on advisory boards for Celgene, Millennium, Johnson & Johnson, Novartis, Bristol-Myers Squibb and Onyx. JC, HEJ, AJ, LP, HE, JH, IT, AM, JW, JL, SK, VR and BD have nothing to disclose.

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