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REVIEW

Lenalidomide for the treatment of relapsed and refractory multiple myeloma

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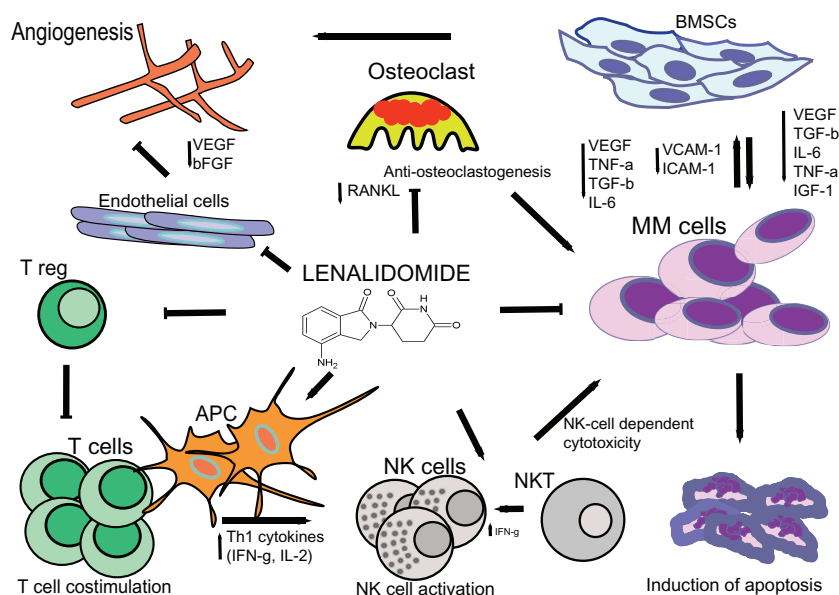Email n.w.c.j.vandedonk@umcutrecht.nl

Abstract: Lenalidomide is an amino-substituted derivative of thalidomide with direct antiproliferative and cytotoxic effects on the myeloma tumor cell, as well as antiangiogenic activity and immunomodulatory effects. Together with the introduction of bortezomib and thalidomide, lenalidomide has significantly improved the survival of patients with relapsed and refractory myeloma. The most common adverse events associated with lenalidomide include fatigue, skin rash, thrombocytopenia, and neutropenia. In addition, when lenalidomide is combined with dexamethasone or other conventional cytotoxic agents, there is an increase in the incidence of venous thromboembolic events. There is now evidence that continued treatment with lenalidomide has a significant impact on survival by improving the depth and duration of response. This highlights the value of adverse event management and appropriate dose adjustments to prevent toxicity, and of allowing continued treatment until disease progression. In this review, we will discuss the different lenalidomide-based treatment regimens for patients with relapsed/refractory myeloma. This is accompanied by recommendations of how to manage and prevent adverse events associated with lenalidomide-based therapy.

Keywords: lenalidomide, multiple myeloma, immunomodulatory drugs, relapse treatment, refractory disease

Introduction

Lenalidomide and pomalidomide, as more potent derivatives of thalidomide, have been found to be less toxic and more active than their parent drug in the treatment of multiple myeloma (MM).[1–4] Because of the structural similarities between thalidomide and its derivative immunomodulatory drugs (IMiDs), these agents have similar modes of action with both direct antitumor activity and indirect immunomodulatory and antiangiogenic effects (Figure 1). IMiDs directly kill MM cells by the induction of cell cycle arrest and caspase-dependent apoptosis.[5–7] In addition, we have shown that IMiDs target a subpopulation of MM cells with stem cell-like features (ie, side-population cells).[8] Recently, it has been demonstrated that cereblon, the primary target for thalidomide teratogenicity,[9] is required for the cytotoxic effects of thalidomide, lenalidomide, and pomalidomide.[10]

In addition, lenalidomide also impairs MM cell survival and proliferation through interference with the protective properties of bone marrow stromal cells, including the down-regulation of adhesion molecules such as VCAM-1 and ICAM-1,[11,12] and inhibition of the production of cytokines like IL-6 and TNF-α.[13] Furthermore, IMiDs inhibit angiogenesis by downregulation of vascular endothelial growth factor and β–fibroblast growth factor[14,15] and impair osteoclastogenesis by reducing RANKL levels.[16] IMiDs also

Angiogenesis

Osteoclast

BMSCs

VEGF
bFGF

Anti-osteoclastogenesis

VEGF
TNF-a
TGF-b
IL-6

VCAM-1
ICAM-1

VEGF
TGF-b
IL-6
TNF-a
IGF-1

RANKL

Endothelial cells

MM cells

T reg

LENALIDOMIDE

NH₂

APC

NK-cell dependent
cytotoxicity

T cells

NK cells

NKT

IFN-g

Th1 cytokines
(IFN-g, IL-2)

T cell costimulation

NK cell activation

Induction of apoptosis

Figure 1 The proposed mechanisms of action of lenalidomide in multiple myeloma include immune modulation (**A**); interference with tumor microenvironment interactions (**B**); and direct antitumor effects (**C**). (**A**) Immunomodulation by lenalidomide includes T cell co-stimulation, suppression of Tregs, increased production of Th1 cytokines, and activation of NK and NKT cells. (**B**) Lenalidomide mediates disruption of myeloma cell-microenvironment interactions via several mechanisms including antiangiogenesis, anti-inflammatory effects, antiosteoclastogenic properties, modulation of cytokine production, and downregulation of adhesion molecules. (**C**) IMiDs also exert direct effects on myeloma cells via cell cycle arrest and induction of apoptosis.
Abbreviations: T reg, regulatory T cell; BMSCs, bone marrow stromal cells; APC, antigen-presenting cell; NK cells, natural killer cells; NKT cells, natural killer T cells; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; RANKL, receptor activator of nuclear factor kappa-B ligand; bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor-β; IGF-1, insulin-like growth factor 1; TNF-α, tumor necrosis factor α; IL-6, interleukin-6.

have immunomodulatory effects including stimulation of T cell proliferation, increased production of IL-2 and IFNγ,[13] and enhancement of cytotoxic T lymphocyte, natural killer T, and natural killer effector cell activity against MM cells.[17,18] Lenalidomide is more potent than thalidomide in both stimulating T cell proliferation via the T cell receptor and in enhancing IL-2 and IFNγ production. IMiDs also decrease the development of regulatory T cells in MM.[19] In addition, lenalidomide inhibits myeloid cell-mediated inflammatory function by decreasing the secretion of IL-6, TNFα, and IL-10.[20] We have demonstrated that IMiDs induce immune effector cell activation by triggering positive costimulatory molecule CD28 signaling in T cells,[17,21] as well as regulate cytokine signaling by downregulating the suppressor of cytokine signaling (SOCS)1 in immune effector cells in MM, thereby inducing IL-2 and IFNγ production.[22]

In this review, we will discuss the clinical activity and optimal use of lenalidomide and lenalidomide-based combinations in the management of relapsed and refractory MM.

Single-agent lenalidomide in relapsed/refractory MM

Single-agent lenalidomide was shown to be effective and well tolerated in relapsed/refractory MM patients who had received a median of three prior regimens as part of a Phase I trial in which the maximum tolerated dose (MTD) was found to be 25 mg daily, and 29% of the patients obtained at least a partial response (PR).[4] Importantly, no significant somnolence, constipation, or neuropathy was observed. The most common adverse events included fatigue, skin rash, thrombocytopenia, and neutropenia, which proved manageable with dose-reduction and granulocyte colony stimulating factor (G-CSF) support.[4] Single-agent lenalidomide did not significantly increase the risk of venous thromboembolism (VTE).[4] Other studies have since confirmed that single-agent lenalidomide has a favorable tolerability and promising efficacy, even after prior treatment with thalidomide, bortezomib, and/or high-dose melphalan with autologous stem cell rescue.[23,24]

Lenalidomide plus dexamethasone in relapsed/refractory MM

In vitro studies demonstrated that dexamethasone enhances the anti-MM effects of lenalidomide.[5,6] Based on these preclinical and early phase clinical trial data suggesting that response rates can be markedly enhanced by the addition of dexamethasone, two randomized Phase III trials (MM-009 and MM-010) compared lenalidomide (25 mg on days 1–21

of a 28-day cycle) plus dexamethasone (40 mg on days 1–4, 9–12, and 17–20 for the first four cycles, and 40 mg on days 1–4 thereafter) with placebo plus dexamethasone in relapsed/ refractory MM patients who had received a median of two previous therapies (Table 1). Dimopoloulos et al[25] demonstrated the superior efficacy of lenalidomide-dexamethasone compared with placebo plus dexamethasone in terms of higher overall response rate (complete response (CR) + PR; 60.2% vs 24.0%; $P < 0.001$) and CR rate (15.9% vs 3.4%; $P < 0.001$). The authors also noted that lenalidomide-dexamethasone exhibited a longer median time to progression (TTP) (11.3 vs 4.7 months; $P < 0.001$) and median overall survival (OS) (not reached and 20.6 months; $P = 0.03$) when compared with placebo plus dexamethasone. In the study of Weber et al,[26] comparable results were reported with a superior response rate (≥PR: 61.0% vs 19.9%; $P < 0.001$), CR rate (14.1% vs 0.6%; $P < 0.001$), median TTP (11.1 vs 4.7 months; $P < 0.001$), and median OS (29.6 vs 20.2 months; $P < 0.001$) in the lenalidomide-dexamethasone group when compared to the placebo-dexamethasone group. Adverse events associated with lenalidomide therapy were neutropenia, thrombocytopenia, and thromboembolic complications in both studies.[25,26] There was a non-significant trend toward increased grade 3 or 4 infections in lenalidomide recipients.[25,26]

Pooled analysis of both randomized Phase III trials with an extended median follow-up of 48 months demonstrated a continued prolongation of overall survival for the lenalidomide-dexamethasone group (38.0 months) versus the dexamethasone single-agent group (31.6 months), despite a crossover of 48% of the patients to either lenalidomide or lenalidomide plus dexamethasone as subsequent salvage therapies.[27]

Response to lenalidomide plus dexamethasone improved over time, with better quality of response associated with improved clinical outcomes. Median TTP and OS were longer in patients who achieved CR/very good partial response (VGPR) compared to patients who obtained a PR (TTP: 27.7 vs 12.0 months; OS: not yet reached vs 44.2 months).[28] San Miguel et al showed that patients who participated in MM-009 or MM-010 who achieved PR or better and continued therapy had an overall survival of 50.9 months, compared to 35.0 months in patients who discontinued lenalidomide-dexamethasone due to adverse events, withdrawal of consent, or other reasons.[29,30] This suggests that continued treatment has a significant impact on survival, possibly by improving the depth of response.

Preliminary results from another pooled analysis of both Phase III studies showed that patients whose dexamethasone

Table 1 Results from the two Phase III studies evaluating lenalidomide plus dexamethasone versus placebo plus dexamethasone

Study	Regimen	Schedule	N	≥PR	CR	TTE	Key toxicities
Dimpopoulos et al (MM-010)[25]	Len-dex	Len 25 mg on days 1–21 of 28-day cycle Dex 40 mg on days 1–4, 9–12, 17–20 for the first four cycles, thereafter 40 mg days 1–4	176	60.2%	15.9%	Median TTP: 11.3 months Median OS: not reached	Grade ≥ 3 venous thromboembolism: 11.4% Grade ≥ 3 neutropenia: 29.5% Grade ≥ 3 infection: 11.3%
	Dex	Dex 40 mg on days 1–4, 9–12, 17–20 for the first four 4-week cycles, thereafter 40 mg days 1–4	175	24.0%	3.4%	Median TTP: 4.7 months Median OS: 20.6 months	Grade ≥ 3 venous thromboembolism: 4.6% Grade ≥ 3 neutropenia: 2.3% Grade ≥ 3 infection: 6.2%
Weber et al (MM-009)[26]	Len-dex	Len 25 mg on days 1–21 of 28-day cycle Dex 40 mg on days 1–4, 9–12, 17–20 for the first four cycles, thereafter 40 mg days 1–4	177	61.0%	14.1%	Median TTP: 11.1 months Median OS: 29.6 months	Grade ≥ 3 venous thromboembolism: 14.7% Grade ≥ 3 neutropenia: 41.2% Grade ≥ 3 infection: 21.4%
	Dex	Dex 40 mg on days 1–4, 9–12, 17–20 for the first four 4-week cycles, thereafter 40 mg days 1–4	176	19.9%	0.6%	Median TTP: 4.7 months Median OS: 20.2 months	Grade ≥ 3 venous thromboembolism: 3.4% Grade ≥ 3 neutropenia: 4.6% Grade ≥ 3 infection: 12.0%

Abbreviations: CR, complete response; PR, partial response; TTE, time to events; TTP, time to progression; OS, overall survival; Len, lenalidomine; Dex, dexamethasone.

dose was reduced because of toxicity had a better outcome compared with patients who continued on high-dose dexamethasone.[31] In newly diagnosed MM, lenalidomide combined with low-dose dexamethasone was also associated with lower toxicity and better overall survival than lenalidomide with high-dose dexamethasone;[32] this has been widely adopted, even in the relapsed/refractory MM setting. An appropriate approach to minimize treatment-related toxicity in case of an aggressive relapse (eg, with hypercalcemia or renal failure) is to start with high-dose dexamethasone for rapid disease control, which can be followed by low-dose dexamethasone in case of response. Another subanalysis showed that patients with progression-free survival (PFS) ≥12 months who had dose reductions of lenalidomide after ≥12 months had better PFS than those who had earlier dose reductions or no dose reductions.[33] This suggests that it is important to continue full-dose lenalidomide therapy for at least 12 months in patients who tolerate the treatment, and after this time, the dose can be reduced without compromising treatment efficacy. Overall, these studies highlight the value of adverse event management and appropriate dose adjustments to prevent toxicity, thereby allowing continued treatment until disease progression.

Efficacy of lenalidomide plus dexamethasone and previous treatment

Stadtmauer et al[34] showed in a subset analysis of both Phase III trials that lenalidomide-dexamethasone was more effective in terms of response, TTP, PFS, and OS in patients who had one prior therapy when compared to those who had two or more earlier therapies, indicating that the greatest benefit occurs with early use of lenalidomide-dexamethasone in relapsed/refractory MM. Another pooled analysis of all patients that participated in these randomized trials showed that lenalidomide-dexamethasone was more effective than dexamethasone alone in both thalidomide-exposed and naïve patients.[35] However, higher efficacy in terms of overall response rate, TTP, and PFS of the combination of lenalidomide-dexamethasone or dexamethasone alone was observed in thalidomide-naïve patients compared to thalidomide-exposed patients, suggesting some degree of cross-resistance between thalidomide and lenalidomide. However, patients previously treated with thalidomide had significantly more prior lines of therapy compared with patients who were thalidomide naïve.[35] A French study showed similar results with inferior TTP and OS for patients that previously progressed on thalidomide.[36] In contrast, an Italian study showed that response, PFS, and OS were similar between thalidomide-resistant and thalidomide-sensitive

patients.[37] A retrospective analysis performed in The Netherlands further showed that response rate was not influenced by previous thalidomide or bortezomib treatment.[38]

In the MM-009 study, the response (≥PR) to lenalidomide-dexamethasone was 68% in bortezomib exposed and 60% in bortezomib naïve patients.[26] Results from the VISTA study also showed that lenalidomide-based therapy is equally effective in patients with or without previous bortezomib treatment.[39] In contrast, a French study highlighted that previous bortezomib exposure was associated with significantly shorter PFS and OS in patients treated with lenalidomide-dexamethasone when compared to patients with no earlier bortezomib treatment. However, patients who received bortezomib had a median of two additional lines of therapy, compared to patients who did not receive bortezomib.[36] Some other studies also suggest that prior bortezomib treatment is associated with lower efficacy of lenalidomide-dexamethasone.[40–42] A retrospective single-center study showed that use of both thalidomide and bortezomib prior to lenalidomide-dexamethasone was associated with a significant reduction in TTP and OS.[41]

Regimens with lenalidomide and conventional cytotoxic agents

Various other lenalidomide-based regimens have been studied to further improve the outcome of patients with relapsed/refractory MM (Table 2). Lenalidomide in combination with adriamycin and dexamethasone (RAD) in refractory and relapsed MM resulted in a high response rate of 73% (≥PR) including 15% CR and 45% VGPR, with hematologic toxicity and infections as the primary side effects.[43] Another lenalidomide and chemotherapy combination tested in the setting of relapsed/refractory MM was lenalidomide combined with pegylated liposomal doxorubicin, vincristine, and dexamethasone with an overall response rate (≥PR) of 75% including 29% CR or near CR.[44] Myelosuppression, neuropathy, muscle cramps, and rash were the most common adverse events. Median PFS was 12 months, and median OS had not been reached at the time of publication.

Preliminary results from a phase I/II study show that the combination of lenalidomide with bendamustine and dexamethasone is effective and well tolerated.[45] Responses were also achieved in patients with prior exposure to lenalidomide. A variation on this regimen, bendamustine-lenalidomide plus prednisone followed by lenalidomide maintenance was evaluated in another Phase I trial. Preliminary results show that this combination was well tolerated and active in the setting of relapsed/refractory disease.[46]

Table 2 Results from selected studies (n ≥ 30) in relapsed/refractory MM evaluating combinations of lenalidomide with conventional cytotoxic agents

Study	Type of study	Regimen	Schedule	N	Prior treatment	Response	TTE	Key toxicities
Knop et al[43]	Phase I/II	RAD	MTD not reached; highest dose-level: Len 25 mg on days 1–21 of 28-day cycle Doxo 9 mg/m² on days 1–4 Dex 40 mg on days 1–4 and 17–20	69	Median: 2 Thal: 20% Bort: 57% Len: 0%	All evaluable patients ≥PR: 73% VGPR: 45% CR: 15%	Median TTP: 45 weeks Median PFS: 40 weeks 1-year OS: 88%	% of patients Grade ≥ 3 neutropenia: 48% Grade ≥ 3 thrombocytopenia: 38% Grade ≥ 3 anemia: 17% Grade ≥ 3 neurotoxicity: 0% Grade ≥ 3 venous thromboembolism: 2%
Baz et al[44]	Phase I/II	Len-DVD	MTD: Len 10 mg on days 1–21 of 28-day cycle PLD 40 mg/m² on day 1 VCR 2 mg on day 1 Dex 40 mg on days 1–4	62	Median: 3 Thal: 66% Bort: 26% Len: 0%	All evaluable patients ≥PR: 75% CR/nCR: 29%	Median PFS: 12 months Median OS: not reached	% of patients Grade ≥ 3 neutropenia: 32% Grade ≥ 3 thrombocytopenia: 13% Grade ≥ 3 anemia: 3% Grade ≥ 3 peripheral neuropathy: 5% Grade ≥ 3 venous thromboembolism: 9%
Reece et al[50]	Phase I/II	CPR	MTD not reached; highest dose-level: Cyclo 300 mg/m² po on days 1, 8, 15 of 28-day cycle Len 25 mg on days 1–21 Pred 100 mg every other day	32	Median: 2 Thal: 28% Bort: 50% Len: 0%	All evaluable patients ≥MR: 94%	1-year PFS: 78% 1-year OS: 93%	% of patients Grade ≥ 3 neutropenia: 29% Grade ≥ 3 thrombocytopenia: 22% Grade ≥ 3 anemia: NA Grade ≥ 3 neurotoxicity: NA Grade ≥ 3 venous thromboembolism: 6%
Schey et al[49]	Phase I/II	CRD	MTD: Cyclo 600 mg po on days 1, 8 of 28-day cycle Len 25 mg on days 1–21 Dex 20 mg on days 1–4, 8–11 Nine cycles, followed by Len maintenance	31	Median: 3 Thal: 90% Bort: 26% Len: 0%	All evaluable patients ≥PR: 81% VGPR: 7% CR: 29%	Median PFS: not reached 2-year PFS: 56% Median OS: not reached OS at 30 months: 80%	% of patients Grade ≥ 3 neutropenia: 19% Grade ≥ 3 thrombocytopenia: NA Grade ≥ 3 anemia: NA Grade ≥ 3 neurotoxicity: 0% Grade ≥ 3 venous thromboembolism: 6%
Lentzsch et al[45]	Phase I/II	BLD	MTD: Len 10 mg day 1–21 of a 28-day cycle Bendamustine 75 mg/m² on days 1 and 2 Dex 40 mg on days 1, 8, 15, 22	36	Median: 3 Thal: 48% Bort: NA Len: 79%	All evaluable patients ≥PR: 52 VGPR: 24% CR: 0%	Median PFS: 4.4 months Median OS: not reached	% of patients Grade 4 neutropenia: 24.1% Grade 4 thrombocytopenia: 7%

Abbreviations: MM, multiple myeloma; CR, complete response; nCR, near-complete response; VGPR, very good partial response; PR, partial response; NA, not available; TTE, time to events; TTP, time to progression; PFS, progression-free survival; OS, overall survival; Len, lenalidomide; Len-DVD, lenalidomide, pegylated liposomal doxorubicin, vincristine, and dexamethasone; MTD, maximum tolerated dose; po, oral administration; CRD, cyclophosphamide, lenalidomide, and dexamethasone; BLD, bendamustine, lenalidomide, and dexamethasone; Bort, bortezomib; Thal, thalidomide; Dex, dexamethasone; Pred, prednisone; Doxo, doxorubicin; Cyclo, cyclophosphamide; VCR, vincristine; PLD, pegylated liposomal doxorubicin.

A retrospective study showed that the fully oral combination of lenalidomide (10 mg) with continuous low-dose cyclophosphamide (Endoxan, Baxter 100 mg orally [po]) and prednisone (REP) had a remarkably high activity with good tolerability in lenalidomide/dexamethasone-refractory MM (≥minimal response (MR): 64%; median PFS: 12.2 months).[47] The efficacy of cyclophosphamide combined with lenalidomide and corticosteroids has also been described by Morgan et al.[48] In a retrospective analysis, they treated relapsed lenalidomide-naïve MM patients with the combination of lenalidomide (25 mg; 21 days, followed by 1 week rest), cyclophosphamide (500 mg po; days 1, 8, 15, 21), and dexamethasone (40 mg po; days 1–4 and 12–15 of a 28-day cycle; RCD regimen) resulting in ≥MR in 75% of patients.[48] However, progression-free survival of 5.7 months seems inferior to REP (12.2 months). The prolonged progression-free survival of patients treated with the REP regimen may be attributed to the continuous exposure of tumor cells to antimyeloma agents in this regimen, which possibly prevents the emergence of resistant clones.

Based on the promising results from these retrospective studies, a prospective Phase I/II study of cyclophosphamide, lenalidomide, and dexamethasone was performed in relapsed/refractory lenalidomide-naïve MM with a median of three previous lines of therapy. The MTD was established at lenalidomide 25 mg on days 1–21, cyclophosphamide 600 mg on days 1 and 8, and dexamethasone 20 mg on days 1–4 and 8–11 of each 28-day cycle. Hematological toxicity could be easily managed by dose-reductions. Of all 31 evaluable patients, 81% achieved at least PR, including 29% CR.[49] The PFS at 2 years was 56%, and the OS at 30 months was 80%.[49] Another Phase I/II study is currently evaluating the combination of lenalidomide plus prednisone and cyclophosphamide, and has enrolled 32 lenalidomide-naïve patients.[50] Preliminary data show good tolerability with high efficacy.

Regimens with lenalidomide plus proteasome inhibitor

In vitro studies demonstrate that lenalidomide sensitizes MM cells to bortezomib-induced apoptosis, which provided the rationale for clinical studies evaluating this combination (Table 3).[6] A Phase I dose-escalation trial evaluated lenalidomide plus bortezomib in relapsed and refractory MM (median of five prior lines of therapy, including 87% of the patients with prior thalidomide, 55% with prior bortezomib, and 18% prior lenalidomide). Dexamethasone was added if the patient experienced progression after the second cycle. The MTD was lenalidomide 15 mg (days 1–14

of a 21-day cycle) and bortezomib 1.0 mg/m^2 (days 1, 4, 8, 11).[51] MR or better was observed in 61% of the patients, which included 39% ≥ PR and 8% CR or near-CR. The most common treatment-related grade 3 to 4 toxicities included reversible neutropenia, thrombocytopenia, and anemia.[51] This study was followed by a Phase II trial, which evaluated the efficacy of this combination at the MTD in 64 patients with relapsed or refractory disease. Preliminary results show an impressive overall response rate (≥MR) of 78%, including 64% ≥ PR and 25% CR plus near-CR.[52]

Similar results were obtained in a Greek study, which demonstrated that the addition of bortezomib to lenalidomide-dexamethasone was associated with a high response rate of at least PR in 63% of patients (median of two previous lines of therapy).[53] Thalidomide-refractory disease was associated with an inferior response rate and survival.[53] Another study evaluated lenalidomide, bortezomib, and dexamethasone followed by lenalidomide-dexamethasone maintenance as treatment of first relapse after autologous stem cell transplantation. Preliminary data showed a promising response rate (≥PR: 71%; ≥VGPR: 43%) with a low toxicity profile.[54]

The addition of pegylated doxorubicin to a modified schedule of lenalidomide-bortezomib-dexamethasone was evaluated in a Phase II study in relapsed/refractory MM. At least PR was achieved in 10 (56%) of 18 patients (median of four lines of prior therapy).[55]

A dose-escalation study is investigating lenalidomide plus carfilzomib and dexamethasone in MM patients who have received a median of three previous therapies. Preliminary results show a response rate (≥PR) of 55% across all cohorts.[56] Responses were also observed in patients who had prior therapy with bortezomib or lenalidomide.

Lenalidomide-dexamethasone in combination with MLN9708, an oral, potent, reversible proteasome inhibitor, is currently being evaluated in newly diagnosed MM (NCT01217957 and NCT01383928). In addition, a phase III trial of weekly MLN9708, lenalidomide, and dexamethasone in patients with relapsed/refractory MM will soon be initiated (NCT01564537).

Regimens with lenalidomide and thalidomide

Based on a minimal overlapping side effect profile and different mechanisms of action between thalidomide (more antiangiogenic activity) and lenalidomide (more potent antiproliferative, cytotoxic, and immunomodulatory effects) in preclinical studies, the four-drug combination of lenalidomide, melphalan, prednisone, and thalidomide

Table 3 Results from selected studies in relapsed/refractory MM evaluating combinations of lenalidomide with other novel agents (IMiDs and proteasome inhibitors)

Study	Type of study	Regimen	Schedule	N	Prior treatment	Response	TTE	Key toxicities
Richardson et al[51]	Phase I	RVD	MTD: Len 15 mg on days 1–14 of 21-day cycle Bort 1.0 mg/m² on days 1, 4, 8, 11 of 21-day cycle Dex 20 or 40 mg on days 1, 2, 4, 5, 8, 9, 11, 12 in case of progression after two cycles	38	Median: 5 Thal: 87% Bort: 55% Len: 18%	All evaluable patients ≥MR: 61% CR/nCR: 8%	Median TTP: 7.7 months Median OS: 37 months	% of patients Grade ≥ 3 neutropenia: 63% Grade ≥ 3 thrombocytopenia: 45% Grade ≥ 3 anemia: 18% Grade ≥ 3 peripheral neuropathy: 0% Grade ≥ 3 venous thromboembolism: 3%
Richardson et al[52]	Phase II	RVD	Len 15 mg on days 1–14 of 21-day cycle Bort 1.0 mg/m² on days 1, 4, 8, 11 of 21-day cycle Dex 20 or 40 mg (cycles 1–4) or 10 or 20 mg (cycles 5–8) on days 1, 2, 4, 5, 8, 9, 11, 12 After 8 cycles responding patients could receive maintenance: Len on days 1–14 of 21-day cycle Bort on days 1 and 8 Dex on days 1, 2, 8, 9	64	Median: 2 Thal: 73% Bort: 53% Len: 6%	All evaluable patients ≥MR: 78% ≥PR: 64% nCR/CR: 25%	Median TTP: 9.5 months Median PFS: 9.5 months Median OS: 26 months	% of patients Grade ≥ 3 neutropenia: 30% Grade ≥ 3 thrombocytopenia: 22% Grade ≥ 3 anemia: NA Grade ≥ 3 peripheral neuropathy: 3% Grade ≥ 3 venous thromboembolism: 0%
Dimopoulos et al[53]	Phase II	RVD	Len 15 mg on days 1–14 of 21-day cycle Bort 1.0 mg/m² on days 1, 4, 8, 11 of 21-day cycle Dex 40 mg on days 1–4 After 8 cycles patients without progression continued with: Len on days 1–21 of 28-day cycle Dex 40 mg on days 1–4	49	Median: 2 Thal: 80% Bort: 88% Len: 0%	All evaluable patients ≥PR: 63% VGPR: 14% CR: 6%	Median PFS: 7 months Median OS: 16 months	% of patients Grade ≥ 3 neutropenia: 26% Grade ≥ 3 thrombocytopenia: 14% Grade ≥ 3 anemia: 20% Grade ≥ 3 peripheral neuropathy: 14% Grade ≥ 3 venous thromboembolism: 4%
Palumbo et al[57]	Phase II	RMPT	Len 10 mg days 1–21 of a 28-day cycle Mel 0.18 mg/kg po on days 1–4 Pred 2 mg/kg on days 1–4 Thal 50 mg or 100 mg on days 1–28 After 6 cycles maintenance with len 10 mg on days 1–21 of 28-day cycle	44	Median: 1 Thal: 23% Bort: 20% Len: 0%	All evaluable patients ≥PR: 75% VGPR: 32% CR: 2%	1-year PFS: 52% 1-year OS: 72%	% of patients Grade ≥ 3 neutropenia: 63% Grade ≥ 3 thrombocytopenia: 34% Grade ≥ 3 anemia: 34% Grade ≥ 3 neurotoxicity: 0% Grade ≥ 3 venous thromboembolism: 0%
Shah et al[58]	Phase I	RTD	MTD: Len 25 mg days 1–21 of 28-day cycle Thal 100 mg days 1–28 Dex 40 mg on days 1–4, 9–12, and 17–20 of cycles 1–2; thereafter 40 mg on days 1, 8, 15, 21	18	Median: 3 Thal: NA Bort: NA Len: NA	All evaluable patients ≥PR: 92% VGPR: 23% nCR: 15%	Median PFS: NA Median OS: NA	DLTs: steroid-induced toxicity; rash due to thalidomide plus atrial fibrillation; hypertensive crisis and volume overload due to dexamethasone

(*Continued*)

Table 3 (Continued)

Study	Type of study	Regimen	Schedule	N	Prior treatment	Response	TTE	Key toxicities
Berenson et al[55]	Phase II	DVD-R	Len 10 mg on days 1–14 of a 28-day cycle Bort 1.0 mg/m² on days 1, 4, 8, 11 Dex 40 mg on days 1, 4, 8, 11 PLD 4.0 mg/m² on days 1, 4, 8, 11	18	Median: 4 Thal: 50% Bort: 89% Len: 33%	All evaluable patients ≥PR: 56% VGPR: 28% CR: 6%	Median PFS: NA Median OS: NA	% of patients Grade ≥ 3 neutropenia: 17% Grade ≥ 3 thrombocytopenia: 22% Grade ≥ 3 anemia: 11% Grade ≥ 3 neurotoxicity: 6% Grade ≥ 3 venous thromboembolism: NA
Niesvizky et al[56]	Phase Ib	CRd	MTD not yet reached: Car 15–27 mg/m² on days 1, 2, 8, 9, 15, 16 of a 28-day cycle Len 10–25 mg on days 1–21 Dex 40 mg on days 1, 8, 15, 22 of cycles 1–4; thereafter 40 mg on day 1	32	Median: 2.5 Thal: 46% Bort: 77% Len: 54%	All evaluable patients ≥PR: 55% VGPR: 20% CR: 10%	Median PFS: NA Median OS: NA	% of patients Grade ≥ 3 neutropenia: 8% Grade ≥ 3 thrombocytopenia: 15% Grade ≥ 3 anemia: 15% Grade ≥ 3 neurotoxicity: 0% Grade ≥ 3 venous thromboembolism: NA

Abbreviations: MM, multiple myeloma; CR, complete response; nCR, near-complete response; PR, partial response; NA, not available; TTE, time to events; TTP, time to progression; EFS, event-free survival; OS, overall survival; Len, lenalidomide; Bort, bortezomib; Thal, thalidomide; Dex, dexamethasone; Pred, prednisone; Doxo, doxorubicin; Cyclo, cyclophosphamide; Mel, melphalan; Car, carfilzomib; po, oral administration; RVD, lenalidomide, bortezomib, and dexamethasone; RMPT, lenalidomide, melphalan, prednisone, and thalidomide; RTD, lenalidomide, thalidomide, and dexamethasone; DVD-R, pegylated liposomal doxorubicin, bortezomib, dexamethasone, and lenalidomide; CRd, carfilzomib, lenalidomide, and dexamethasone; MTD, maximum tolerated dose.

was tested in refractory/relapsed lenalidomide-naïve MM (Table 3).[57] A high response rate was observed, with 75% of the 44 patients achieving at least a PR, including 32% VGPR and 2% CR. Combining thalidomide with lenalidomide seems to increase the hematologic toxicity when compared to lenalidomide alone.

Another combination of both IMiDs is lenalidomide, thalidomide, and dexamethasone[58] (Table 3). This combination was active, with at least PR in 12 out of 13 (92%) evaluable patients (median of three prior lines of therapy). Interestingly, seven of eight patients (88%) with lenalidomide-refractory disease achieved at least a PR, suggesting that thalidomide may modulate lenalidomide resistance.

Regimens with lenalidomide and new novel agents
mTor inhibitors

In vitro studies demonstrating synergistic antimyeloma activity between lenalidomide and mTor inhibitors[59] provided the rationale for testing the combination of lenalidomide and temsirolimus in a Phase I trial in relapsed/refractory MM patients (n = 21, median of three previous lines of therapy including 19% lenalidomide). The maximum tolerated dose was lenalidomide 25 mg on days 1–21 of a 28-day cycle with 15 mg of temsirolimus weekly. Most common adverse events included fatigue, neutropenia, anemia, rash, and electrolyte abnormalities. The combination had modest activity, with PR in only two patients, and stable disease in 15 patients.[60]

Another Phase I study evaluated RAD001 and lenalidomide in relapsed/refractory MM (28 patients with a median of four previous therapies, including 50% prior lenalidomide).[61] At least PR was obtained in 11% of patients.

Histone deacetylase inhibitors

A Phase I trial is evaluating vorinostat, lenalidomide plus dexamethasone in patients with relapsed/refractory MM.[62] Patients had received a median of four prior therapies including lenalidomide in 45%, thalidomide in 71%, and bortezomib in 65% cases. Fatigue, cytopenias, and diarrhea were the most common adverse events. At least PR was achieved in 53% of patients, including those previously exposed to lenalidomide. Median TTP was 5 months.

The combination of vorinostat, lenalidomide, and dexamethasone as a salvage therapy was also evaluated in 29 lenalidomide-dexamethasone-refractory MM patients with a median of four previous lines of therapy.[63] At least PR

was achieved in 24% of patients, with a median duration of response of 4 months. Common toxicities included fatigue, myelosuppression, and diarrhea.

Akt inhibitor

Perifosine, an oral Akt inhibitor, was combined with lenalidomide and dexamethasone in a Phase I trial.[64] Patients had received a median of two prior lines of treatment, and patients refractory to lenalidomide plus dexamethasone were excluded. A total of 50% of the patients achieved at least PR, and median PFS was 10.8 months.

Lenalidomide and monoclonal antibody therapy

The ability of lenalidomide to activate multiple arms of the patient's immune system including enhanced antibody-dependent cell-mediated cytotoxicity,[65,66] coupled with its ability to modulate important signaling cascades in MM cells, forms the rationale to combine lenalidomide with monoclonal antibodies.[67] Preliminary results from ongoing trials show encouraging results with acceptable toxicity for lenalidomide combined with elotuzumab (anti-CS1 antibody),[68,69] lorvotuzumab mertansine (anti-CD56 antibody conjugated to DM1),[70] and dacetuzumab (anti-CD40 antibody).[71]

In vitro studies also demonstrated enhanced cytotoxicity of NK cells against MM cells of the combination of NK cell activating antibodies and lenalidomide, which also activates NK cells.[72] Based on these data, a Phase I/II trial is currently evaluating lenalidomide combined with 1-7F9, a fully human anti-KIR antibody, in relapsed/refractory MM.[72]

Lenalidomide and cancer vaccines

Suppression of cytotoxic T cells by cytokines such as TGF-β, recruitment of regulatory T cells, and altered expression of immune suppressor molecules on MM cells or immune effector cells, contributes to immune evasion in MM. In addition, the function of dendritic cells and NK cells is severely impaired in MM. In a mouse model, a lymphoma vaccine in combination with lenalidomide improved survival when compared to vaccine or lenalidomide alone. Lenalidomide treatment was accompanied with enhanced cellular immunity and ameliorated immune suppression.[73] In vitro studies showed that lenalidomide also enhanced T cell activation in response to stimulation by a dendritic cell/MM fusion vaccine.[74] A recent clinical study in MM patients showed that lenalidomide augmented humoral and cellular responses to the polyvalent pneumococcal vaccine, Prevnar (Wyeth

Pharmaceuticals, Inc, Madison, NJ; Pfizer Inc, New York, NY).[75] Altogether, these studies indicate that lenalidomide has the potential to improve immune dysfunction and can serve as an adjuvant for MM vaccines.

Increasing evidence also suggests that IMiDs enhance the graft-versus-myeloma effect mediated by donor T cells or donor NK cells after allogeneic stem cell transplantation or donor lymphocyte infusions.[76–80] Unfortunately, use of IMiDs in this setting seems also to be associated with increased occurrence of graft-versus-host disease.[78,79]

Cytogenetics

Data from a Canadian study in relapsed or refractory MM suggest that lenalidomide-dexamethasone can overcome the poor prognosis conferred by del(13q) and t(4;14), but not del(17p) (all detected by fluorescence in situ hybridization).[40] However, results from a French multicenter study testing lenalidomide-dexamethasone in the relapsed setting showed an inferior PFS in patients with del(13q) and t(4;14).[36] Also, del(1p21) adversely affected the outcome of patients treated with lenalidomide-dexamethasone.[42]

In other lenalidomide-based combinations, del(17p) remains a negative prognostic factor, with some combinations overcoming poor prognosis of both t(4;14) and del(13q). Response and TTP were identical in patients with or without del(13q) or t(4;14) following RAD treatment, but del(17p) remained associated with an inferior response rate and shortened TTP.[43] In addition, when bortezomib was added to lenalidomide-dexamethasone, del(17p) was still associated with an inferior response rate and survival. But bortezomib added to lenalidomide-dexamethasone overcame part of the adverse impact conferred by del(13q), ampl(1q21), and t(4;14).[53] The PFS of patients treated with lenalidomide, melphalan, prednisone and thalidomide was independent of the presence of del(13q), but was inferior in patients with t(4;14).[57]

Lenalidomide treatment in frail or elderly patients with relapsed/refractory MM

More than half of all new cases of MM occur in patients 65 years of age or older,[81] whereas the proportion of elderly relapsed/refractory MM patients enrolled in clinical trials decreases with age, and no specific trials are currently available for unfit elderly MM patients. Furthermore, during the last decade, the improvement in survival was more pronounced in younger patients,[81] which is likely due to patient characteristics such as lower performance status and comorbidities in

the elderly which strongly impact chemotherapy feasibility and tolerance. In addition, biologic differences between tumors may play a role. This highlights the need for further treatment innovations in this population.

Dose adjustments of lenalidomide and other components of the salvage regimen, such as dexamethasone, are needed to keep patients on therapy and prevent treatment discontinuation. Depending on the number of risk factors (such as age $\geq$ 75 years, frailty, and comorbidities), the starting dose of lenalidomide should be 25, 15, or 10 mg on days 1–21, and the starting dose of dexamethasone should be 40 mg, 20 mg, or 10 mg weekly.[82,83] A Phase II trial in relapsed/refractory MM patients aged $\geq$60 years and/or with a creatinine clearance $<$ 60 mL/min showed that lower doses of lenalidomide (15 mg) and dexamethasone reduced the incidence of hematological toxicities, infections, and VTE without compromising efficacy when compared to standard dose lenalidomide-dexamethasone (MM-010 and MM-009).[84] Another lenalidomide-containing salvage regimen with proven efficacy accompanied with mild toxicity, which may be beneficial to frail MM patients, includes dose-adjusted lenalidomide-cyclophosphamide-prednisone.[47] Careful monitoring of toxicity and prompt administration of supportive care such as G-CSF in case of neutropenia is important in this group of patients.

Renal impairment

Bortezomib clearance is independent of renal function and overcomes the adverse impact of renal dysfunction. Importantly, it also improves renal function to a higher degree than conventional chemotherapy or IMiD-based regimens. This suggests that relapsed/refractory patients presenting with renal insufficiency should receive bortezomib-based treatment. However, in case of bortezomib-refractory disease or intolerance to bortezomib, thalidomide or dose-adjusted lenalidomide-based regimens can be considered.[85]

Lenalidomide is a renally metabolized drug, and without dose adjustments myelosuppression is more frequent in patients with renal impairment.[86–88] In a subgroup analysis of MM-009 and MM-010 studies (starting dose of lenalidomide 25 mg for all patients), response and TTP was independent of renal function. Improvement of renal function was observed in the majority of patients with renal impairment. However, patients with severe renal impairment had a shorter OS.[87]

With dosing of lenalidomide being administered according to creatinine clearance (Table 4), toxicity of lenalidomide

Table 4 Adjustment of lenalidomide dose in case of renal impairment

Creatinine clearance	Lenalidomide (days 1–21 of a 28-day cycle)
$\geq$50 mL/min	25 mg/day (standard dose)
30–50 mL/min	10 mg/day
$\leq$30 mL/min	15 mg/2 days
Dialysis	5 mg/day; on days of dialysis, dose should be administered after dialysis

was independent of renal function.[89] The response rate, PFS, and OS following lenalidomide-dexamethasone were identical between patients with and without renal impairment, and treatment was associated with improvement of renal function. However, a retrospective single center study from Germany with a starting dose of lenalidomide according to renal function showed that TTP following lenalidomide-dexamethasone was significantly shorter in the case of severe renal impairment, probably due to dose interruptions and reductions resulting from toxicity.[41]

Adjusted dose lenalidomide-based therapy can also be administered to patients requiring dialysis, which is effective, but accompanied by a high incidence of neutropenia and infections.[90]

Management of adverse events associated with lenalidomide
Neutropenia

Neutropenia increases the risk of bacterial and fungal infection, and is a common adverse event of lenalidomide treatment. The incidence of grade 3/4 neutropenia in the MM-009 and MM-010 studies was 41.2% and 29.5%, respectively, in lenalidomide plus dexamethasone-treated patients, whereas it was only 4.6% and 2.3%, respectively, in the placebo plus dexamethasone group.[25,26] The risk of developing grade 3/4 neutropenia is higher when lenalidomide is combined with other chemotherapeutic agents such as alkylating drugs (eg, MPR) or doxorubicin (eg, RAD). Extensive previous treatment is also an important risk factor. Therapy-related toxicities including infections may lead to early treatment discontinuations, thereby negatively affecting outcomes.[91] When patients start with lenalidomide-based treatment, the blood counts should be monitored biweekly, but in case of pre-existing cytopenia, weekly monitoring is recommended. Growth factor support, and sometimes dose adjustments and dose interruptions, should be considered in case neutropenia develops (Table 5). Patients at high risk of developing neutropenia

Table 5 Supportive care for the management or prevention of adverse events associated with lenalidomide

Averse event	Supportive care
Neutropenia	G-CSF
Anemia	Red cell transfusion; start of erythropoietin[†]
Thrombocytopenia	Platelet transfusion
Diarrhea	Loperamide
Rash	Limited, localized rash: antihistamines and topical steroids
	Mild but extensive rash: short course of low-dose prednisone
VTE	Thromboprophylaxis (aspirin for patients at standard risk for VTE and LMWH or adjusted-dose warfarin in high-risk patients) is indicated when lenalidomide is combined with dexamethasone or cytotoxic agents

Note: [†]Concomitant use of erythropoietin with lenalidomide-based combinations may increase risk of VTE.
Abbreviations: G-CSF, granulocyte-colony stimulating factor; VTE, venous thromboembolism; LMWH, low molecular weight heparin.

based on patient-, MM-, and treatment-related factors may benefit from primary prophylaxis with G-CSF.

Venous thromboembolism

Lenalidomide used as a single agent does not increase the risk of VTE. However, treatment with lenalidomide plus dexamethasone or cytotoxic agents results in a higher incidence of VTE.[25,26,48] In the MM-009 and MM-010 trials, the incidence of grade 3 and 4 thromboembolic events was 11.4% and 14.7%, respectively, in the lenalidomide plus dexamethasone group, which was significantly higher compared to 4.6% and 3.4%, respectively, in the placebo plus dexamethasone group.[25,26] Importantly, in both studies thromboprophylaxis was not required. Risk factors for thromboembolic events associated with lenalidomide-dexamethasone treatment include high-dose dexamethasone[32,92–94] and concomitant erythropoietin administration.[92,94–96] A subgroup analysis of the MM-009 and MM-010 trials showed an increased rate of VTE during lenalidomide-dexamethasone therapy in previously thalidomide-exposed patients when compared with thalidomide-naïve patients.[35] Interestingly, data suggest that the frequency of VTE may be markedly reduced when bortezomib is combined with IMiD-based regimens with high thrombogenic potential, even when no thromboprophylaxis was administered.[51,97–103]

In addition, patient-related factors such as advanced age, history of VTE, immobilization, inherited thrombophilic disorders, and comorbidities such as diabetes mellitus and cardiac disease, contribute to the development of VTE during

lenalidomide therapy. Patients treated with lenalidomide-dexamethasone who developed a VTE did not experience shorter OS or TTP.[104]

Importantly, with thalidomide and lenalidomide-based combination therapies, prophylactic treatment with aspirin in patients at standard risk for VTE and low molecular weight heparin, or adjusted dose warfarin for high-risk patients reduces the frequency of VTE (Table 5).[93,95,96,105,106]

Secondary malignancies

There have been recent concerns over the use of lenalidomide and the risk of developing second primary malignancies. There is an increased incidence of second primary malignancies in newly diagnosed MM patients receiving lenalidomide plus melphalan/prednisone (MPR).[107,108] In the randomized Phase III, MM-015 study, the 3-year rate of invasive primary tumors was 7% in patients treated with MPR, 7% in patients treated with MPR followed by lenalidomide maintenance (MPR-R), but only 3% in the melphalan/prednisone group.[108] In addition, patients receiving lenalidomide maintenance following high-dose therapy with autologous stem cell rescue had a significantly higher incidence of second primary cancers.[109–112] In the Intergroupe Francophone du Myelome trial, the incidence of second primary cancers was 3.1 per 100 patient-years in the lenalidomide group versus 1.2 per 100 patient-years in the placebo group.[111] In the CALGB study, 3.5% and 4.3% of the patients in the lenalidomide maintenance group developed new hematologic cancers and solid-tumor cancers (excluding nonmelanoma skin cancers), respectively.[112] The corresponding numbers are 0.4% and 2.2% in the placebo group.[112]

A retrospective pooled analysis of 11 clinical trials of lenalidomide-based therapy has addressed this issue in the relapsed/refractory setting;[113] however, in the absence of prospective studies, conclusions regarding the incidence of second primary cancers are more difficult to draw. In a pooled analysis of 3846 relapsed/refractory MM patients treated with lenalidomide as a single agent (7%) or in combination with dexamethasone (93%), the incidence rate (events per 100 patient-years) of invasive second primary malignancies was 2.08, which is comparable to that expected according to the Surveillance, Epidemiology and End Results cancer registry (2.1).[113] The incidence rates (events per 100 patient-years) of second primary malignancies, excluding noninvasive skin cancers, in the MM-009 and MM-010 trials was 1.71 for lenalidomide plus dexamethasone, and 0.91 for placebo plus

dexamethasone. This difference was not statistically significant, and it was also consistent with the expected incidence of invasive cancer in the general population.[113] However, there was an increased occurrence of noninvasive skin cancers in the lenalidomide plus dexamethasone group compared to the dexamethasone only group (incidence rate: 2.40 vs 0.91). Although there is an increased incidence of non-invasive skin cancers in this patient group, there remains a positive risk-benefit profile of lenalidomide plus dexamethasone in relapsed/refractory MM.[113]

Other adverse events

Other common adverse events associated with lenalidomide treatment include thrombocytopenia, anemia, rash, and diarrhea. These toxicities can be managed with dose reductions or interruptions, as well as with the start of appropriate supportive care (Table 5).[114]

Concluding remarks

Lenalidomide plus dexamethasone and other lenalidomide-based combinations are effective treatment options for relapsed/refractory MM patients. Several studies demonstrate that continued treatment with lenalidomide is associated with improved survival. Appropriate dose adjustments and institution of supportive care are therefore very important to enable patients to continue treatment with lenalidomide-based therapies until disease progression.

The introduction of the novel agents, thalidomide, lenalidomide, and bortezomib,[115] and the application of high-dose therapy with autologous stem cell rescue have improved the survival of MM patients. However, event-free and overall survival for patients that are refractory to both an IMiD and bortezomib is only 5 and 9 months, respectively,[116] indicating that new drugs are still needed for continued disease control. Novel agents are currently being evaluated in clinical trials, and include second generation IMiDs such as pomalidomide, and second generation proteasome inhibitors, such as carfilzomib, MLN 9708, and marizomib. Drugs belonging to other classes, such as histone deacetylase inhibitors, Akt inhibitors, mTor inhibitors, and several monoclonal antibodies including elotuzumab and daratumumab, hold promise for improving the outcome of patients with lenalidomide and bortezomib refractory disease.[67,117] Incorporation of biomarker assessment (using techniques such as fluorescence in situ hybridization, gene expression profiling, array based comparative genomic hybridization, single nucleotide polymorphism array, microRNA array, or high throughput sequencing) in future studies in relapsed/refractory MM will help to evaluate

the risk/benefit profile and tailor individualized therapeutic approaches. Altogether, this will hopefully translate to further improvement in outcomes for MM patients.

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Conflict of interest disclosure

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