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Targeting the Proteasome With Bortezomib in Multiple Myeloma: Update on Therapeutic Benefit as an Upfront Single Agent, Induction Regimen for Stem-Cell Transplantation and as Maintenance Therapy

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Abstract

Bortezomib is the first therapeutic inhibitor of the proteasome that has demonstrated a significant clinical response in patients with otherwise refractory or rapidly advancing disease. Bortezomib has received US Federal Drug Administration approval for the treatment of the hematologic malignancies such as multiple myeloma and mantle cell lymphoma. Herein, the use of bortezomib as an upfront therapy, as an induction regimen before stem-cell transplantation and as maintenance therapy in the treatment of multiple myeloma is discussed.

Keywords

multiple myeloma; bortezomib; monotherapy; stem-cell transplantation induction; maintenance therapy

INTRODUCTION

Multiple myeloma (MM) is a plasma cell proliferative disorder characterized by the uncontrolled growth and dysfunction of the malignant cells within the bone marrow.[1,2] MM is the second most common hematological cancer worldwide and accounts for >11,000 deaths each year in the United States.[3,4] Although MM is predominantly a disease of the elderly with an average age of onset of 65–70 years, recent statistics indicate both increasing incidence and younger age of onset. In the United States, >50,000 individuals have MM, and 20,000 new cases are diagnosed each year, whereas worldwide, there are ~74,000 new cases and >45,000 deaths annually. MM remains an incurable disease, and novel treatment approaches are therefore urgently needed to alleviate patient symptoms and to improve overall survival (OS).

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Therapy for MM simultaneously attempts to reduce or eradicate existing disease while also aiming to control disease-related hematologic, bone, and renal complications.[5] The main treatment modalities include cytotoxic chemotherapy to control disease burden and rarely leads to complete remission; corticosteroids such as dexamethasone and prednisone, immunomodulatory agents such as thalidomide and lenalidomide used in newly diagnosed, those with advanced disease who have failed chemotherapy or stem-cell transplantation (SCT) and new biologic agents such as the proteasome inhibitor bortezomib. In most cases, these agents are used in combination with standard chemotherapy agents. For many years, melphalan and prednisone remained the standard therapy for MM, and response rates (RRs) were ~50% with median survival of ~3 years.[6] Recently, autologous SCT has demonstrated promising results in randomized clinical trials as well.[7,8] Patients eligible for SCT typically avoid alkylator-based induction therapy to enable collection of an adequate and functionally viable harvest of stem cells.[9] As initial therapy in newly diagnosed or relapsed patients, SCT is generally not curative but has been shown to prolong survival.[7,8] Additionally, in selected patients, multiple SCTs may be employed. Advanced age and risk factors such as increased β2-microglobulin levels, low serum albumin levels, abnormal cytogenetics, including chromosome 13 deletion, and being refractory to prior treatment are associated with poorer prognosis in MM and may limit treatment options.[10–12] Depending on the treatment regimen used, patients with renal impairment may achieve lower RRs and shorter OS, and there may be greater safety concerns.

Bortezomib is a synthetic, boronyl dipeptide that highly selectively and reversibly inhibits the proteasome and has multiple effects on MM cell lines and primary human MM cells.[13–15] Bortezomib may inhibit the tightly regulated turnover of a number of proteins that malignant plasma cells need for cellular growth and proliferation. Normal, noncancerous cells are not as susceptible to the deleterious effects of bortezomib as are malignant cells. Bortezomib was approved in May 2003 by the US Federal Drug Administration (FDA) for the treatment of patients with relapsed or refractory MM and who had received at least 2 prior lines of therapy and progressed on their last therapy.[16,17] In 2005, bortezomib was approved by the FDA for the treatment of patients with MM who had received at least 1 prior therapy.[18] In December 2006, the FDA approved bortezomib for treatment of mantle cell lymphoma (MCL).[19] Finally, on June 20, 2008, the FDA approved bortezomib for injection as the upfront treatment of patients newly diagnosed with MM based upon an international, multicenter, open-label, active-control trial in previously untreated patients with symptomatic MM.[20] Time-to-progression (TTP) was the primary efficacy end point, whereas OS, progression-free survival (PFS), and RR were the secondary endpoints. Patients were randomized to receive either melphelan + prednisone (MP) or bortezomib + melphelan + prednisone. The trial was stopped after a prespecified interim analysis showing a statistically significant improvement in TTP with the addition of bortezomib to MP (median: 20.7 months) compared with MP (median: 15 months), whereas OS, PFS, and RR also were significantly superior for the bortezomib–MP combination. Bortezomib is generally well tolerated with mild-to-moderate side effects that are manageable and include peripheral neuropathy and thrombocytopenia. The benefit of a bortezomib-based therapy in MM and MCL, diffuse large B-cell lymphoma and the plasma cell dyscrasias Waldenstroms Macro-globulinemia and Systemic Amyloidosis has been recently reviewed.[21]

BORTEZOMIB AS UPFRONT THERAPY IN MULTIPLE MYELOMA

The objective of frontline therapy in most hematologic malignancies is to maximally kill tumor cells to reduce tumor burden in preparation for consolidation therapy with SCT or as a means in itself to generate long-term disease control. In MM, such a therapy is usually followed by high-dose melphalan and autologous SCT. Based upon promising preclinical

studies, the combination of bortezomib with oral dexamethasone demonstrated substantial response in the treatment of relapsed MM shown to be refractory to conventional chemotherapy.[17] The RR to bortezomib was 35%, and median OS was 16 months with a duration of 12 months. Subsequently, bortezomib was compared to high-dose dexamethasone in MM patients with relapsed disease and who had received 1–3 prior therapies.[18] Bortezomib was superior to high-dose dexamethasone with complete response (CR) and partial response (PR) total of 38% vs 18% for DEX and median TTP of 6.2 vs 3.5 months. To assess efficacy and safety of single-agent bortezomib in previously untreated patients with multiple myeloma (MM), San Miguel et al[20] investigated the prevalence of baseline and treatment-emergent polyneuropathy and identified molecular markers associated with response and neuropathy. Among 64 patients, 41% had partial response or better, including 9% complete/near-complete responses; the median duration of response was 8.4 months. RRs did not differ in the presence or absence of adverse cytogenetics. After a median follow-up of 29 months, median time to progression was 17.3 months. Single-agent bortezomib is effective in previously untreated myeloma. Baseline myeloma-associated neuropathy seems more common than previously reported, and bortezomib-associated neuropathy, although a common toxicity, is reversible in most patients. An interesting approach was used by Dispenzieri et al[22] using single-agent bortezomib as induction, maintenance, and reinduction in patients with high-risk MM. Eastern Cooperative Oncology Group (ECOG) trial E2A02 studied single-agent bortezomib and prospectively targeted high-risk patients and was not followed by consolidative autologous SCT. Moreover, in contrast to other studies, patients were not slated for a set number of cycles or therapy followed by high-dose chemotherapy ± peripheral SCT. Among high-risk patients, single-agent bortezomib induced a 51% ORR, which was comparable to that reported by others in unselected patient populations. A limitation in the study was that patients with *t*(4:14) were underrepresented. Although bortezomib was equally efficacious in high-risk and low-risk populations, it does not seem to be the optimal treatment choice to achieve sustained disease free survival in the absence of SCT or high-dose chemotherapy.

BORTEZOMIB AS INDUCTION THERAPY IN STEM-CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

Autologous SCT is considered the gold standard initial therapy for patients <65 years of age who have been diagnosed with MM, because it results in higher rates of CR and longer time of event-free survival.[23] The incorporation of novel agents has resulted in higher pre and posttransplantation CR rates, and induction with bortezomib-containing regimens has shown promising results in those with poor-risk cytogenetics. Conventional induction regimens followed by single or double autologous stem-cell transplantation (ASCT) result in a median survival of 6 years with immunofixation negative CR rates up to 40% under optimal circumstances.[23–25] The combination of thalidomide + dexamethasone (THAL-DEX) is the current FDA approved pretransplantation induction regimen, but numerous strategies that incorporate novel agents such as bortezomib have been and are being investigated. In 2005, Jagannath et al[26] reported results of a phase 2 trial that used the combination of bortezomib + dexamethasone for the treatment of 32 newly diagnosed patients with MM (Table 1). Patients received bortezomib 1.3 mg/m^2 intravenous (IV) on days 1, 4, 8, and 11 every 3 weeks for a maximum of 6 cycles. Twenty-two patients went on to receive dexamethasone (40 mg) added to their regimen on the day of and day after bortezomib administration because they had less than a PR after 2 cycles or less than a CR after 4 cycles. There was an overall response rate (ORR) of 88%, and most patients then received high-dose chemotherapy with peripheral SCT. Harousseau et al[27] used bortezomib + dexamethasone as induction in 48 patients and achieved an ORR of 66%. Treatment regimen consisted of bortezomib 1.3 mg/m^2 IVon days 1, 4, 8, and 11 and 40 mg of dexamethasone on days 1–4

and 9–12 during cycles 1 and 2 and reduced to days 1–4 during cycles 3 and 4. Patients were treated for 4–21 day cycles. Rosinol et al[28] reported newly diagnosed MM patients with 6 alternating cycles of bortezomib and dexamethasone and 60% ORR. The regimen used was bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 alone during cycles 1, 3, and 5 and with dexamethasone (40 mg) on days 1–4, 9–12, 17–20 during cycles 2, 4, and 6. Richardson et al[29] reported treatment of 64 MM patients with single-agent bortezomib and an ORR of 41%, but 32 underwent peripheral stem cell transplant. Importantly, nearly half the patients in this study did not go on to receive SCT, and extended analysis may offer uncomplicated PFS and OS information.

The Intergroupe Francophone Du Myelome 2005-01 trial was conducted with 482 patients and demonstrated statistically significant differences in CR/near-CR (nCR) rates (21% vs 8%, $P = 0.0023$) and ≥VGPR rates (47% vs 19%) to favor the VD (bortezomib + dexamethasone) regimen.[35] The benefit of the bortezomib + dexamethasone arm was maintained after the first auto-SCT. In addition, stem cells were mobilized from recipients who received bortezomib-based induction without additional complications. An update was presented, and the benefit of the bortezomib-based regimen was maintained.[46] Survival results were presented, and though PFS was not significant between the 2 groups (36 vs 30 months), this changed if patients in both cohorts achieved ≥VGPR with induction (41 vs 29 months; $P < 0.001$) or achieved ≥VGPR with transplant (41 vs 33 months; $P = 0.0257$). There was no detectable significant difference in the VD group between patients with advanced stage or poor cytogenetics, although the analysis of patient cytogenetics was not exhaustive. A modified induction regimen of bortezomib/thalidomide/dexamethasone (VTD) using a reduced bortezomib dose of 1.0 mg/m^2 and thalidomide of 100 mg/d (vTD) showed a significant CR + VGPR improvement for the experimental arm with improvement in peripheral neuropathy.[47] An update on this study as well indicated that the median PFS had not been reached, and with a 2-year PFS of 76%, there was no difference from the 3 induction groups. However, patients who received VD induction, VEL–MEL conditioning for auto-SCT and consolidation had a 2-year PFS of 100%.[31]

Because bortezomib in combination with pegylated, liposomal doxorubicin (PLD) was shown to have significant activity against relapsed/refractory MM, this combination was evaluated in previously untreated MM patients who required induction chemotherapy before SCT. The combination of bortezomib and PLD was well tolerated by chemotherapy-naïve patients, and the steroid-free regimen, as seen previously with bortezomib-containing combinations, did not compromise the collection of adequate stem-cell populations for transplantation.[48] The bortezomib-containing regimens TT2 and TT3 have been extensively well characterized and have shown success as well.[49] TT3 used abbreviated induction and consolidation therapies with 2 rather than 4 cycles each in TT2, on the assumption that the addition of bortezomib (V) to DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) in VDT-PACE would be highly synergistic so that comparable antitumor activity would be delivered with fewer cycles. Drug-free phases of TT2 were ‘bridged’ by THAL-DEX in an effort to suppress the potentially MM-stimulatory signals associated with postchemotherapy hematopoietic recovery. Bortezomib was then combined with THAL-DEX in VTD, which was applied in monthly cycles during the first year of maintenance, followed by THAL-DEX for 2 more years. In the case of the newer agent combinations such as MPT (melphalan, prednisone, thalidomide) or MPT with added bortezomib, greater compliance with the intended therapies is at least partially responsible for their unexpected high success rate. Bortezomib, doxorubicin and dexamethasone (PAD) was evaluated as induction before SCT in newly diagnosed MM patients, using bortezomib 1.3 mg/m^2 (PAD1, $N = 21$) or 1.0 mg/m^2 (PAD2, $N = 20$).[30] CR/VGPR rates with PAD1/PAD2 were 62%/42% postinduction and 81%/53% posttransplant. PFS (29 vs 24 months), time to retreatment (36 vs 29 months) and OS (1 year: 100% vs

95%; 2 years: 95% vs73%) were statistically similar but favored PAD1 vs PAD2. Toxicity was lower in PAD2; bortezomib dose reduction may help manage toxicities while retaining efficacy. PAD is highly active as frontline induction in MM.

Preclinical studies have demonstrated that bortezomib has no toxic effects on stem cells, megakaryocytes, or neutrophil precursors and causes only transient and reversible thrombocytopenia and neutropenia.[50] Numerous clinical studies with bortezomib-based induction regimens have demonstrated no adverse impact on peripheral blood stem cell harvest numbers nor on their quality as defined by engraftment times. These regimens seem to be well tolerated and highly active as induction therapy, with high RRs and consistently high CR rates. The standard treatment for patients with MM who are not candidates for high-dose therapy is melphalan and prednisone.[51] The phase 3 study compared the use of melphalan and prednisone with or without bortezomib in previously untreated patients with MM who were ineligible for high-dose therapy. Patients (682 in total) were randomly assigned to receive 9 6-week cycles of melphalan (at a dose of 9 mg/m^2 of body-surface area) and prednisone (at a dose of 60 mg/m^2) on days 1–4, either alone or with bortezomib (at a dose of 1.3 mg/m^2) on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1–4 and on days 1, 8, 22, and 29 during cycles 5–9. The primary end point was the time to disease progression. The time to progression among patients receiving bortezomib plus melphalan–prednisone (bortezomib group) was 24.0 months, as compared with 16.6 months among those receiving melphalan–prednisone alone (control group) (hazard ratio for the bortezomib group, 0.48; $P < 0.001$). Bortezomib plus melphalan–prednisone was superior to melphalan–prednisone alone in patients with newly diagnosed myeloma who were ineligible for high-dose therapy.

Another regimen designed to evaluate the effect of bortezomib as induction therapy before autologous SCT, used lenalidomide as consolidation maintenance in patients with MM.[32] Newly diagnosed patients aged 65–75 years were eligible and induction (PAD) included 4 21-day cycles of bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11), pegylated liposomal doxorubicin (30 mg/m^2 on day 4), and dexamethasone (40 mg/d; cycle 1: days 1–4, 8–11, and 15–18; cycles 2–4: days 1–4). Autologous transplantation was tandem melphalan 100 mg/m^2 (MEL100) and stem-cell support. Consolidation included 4 28-day cycles of lenalidomide (25 mg/d on days 1–21 every 28 days) + prednisone (50 mg every other day), followed by maintenance with lenalidomide (LP-L; 10 mg/d on days 1–21) until relapse. Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation maintenance, was shown to be an effective regimen.

Bortezomib plus melphalan and prednisone (VMP) is significantly better than melphalan + prednisone alone for elderly patients with untreated MM; however, toxic effects are high.[52] This combination was investigated as a novel and less intensive bortezomib-based regimen to maintain efficacy and to reduce toxic effects. MM patients (260) with untreated disease, 65 years and older, from 63 Spanish centers, were randomly assigned to receive 6 cycles of VMP ($n = 130$) or bortezomib plus thalidomide and prednisone (VTP; $n = 130$) as induction therapy. Induction consisted of 1 cycle of bortezomib twice per week for 6 weeks (1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32), plus either melphalan (9 mg/m^2 on days 1–4) or daily thalidomide (100 mg), and prednisone (60 mg/m^2 on days 1–4). The first cycle was followed by 5 cycles of bortezomib once a week for 5 weeks (1.3 mg/m^2 on days 1, 8, 15, and 22) plus the same doses of melphalan plus prednisone and thalidomide plus prednisone. A total of 178 patients completed the 6 induction cycles and were randomly assigned to maintenance therapy (MT) with bortezomib + prednisone ($n = 87$) or bortezomib + thalidomide ($n = 91$) that consisted of 1 conventional cycle of bortezomib for 3 weeks (1.3 mg/m^2 on days 1, 4, 8, and 11) every 3 months, plus either prednisone (50 mg every other day) or thalidomide (50 mg/d), for up to 3 years. Treatment codes were generated with a

computerized random number generator, and neither participants nor study personnel were masked to treatment. The primary endpoint was RR in induction and maintenance phases. Reduced-intensity induction with a bortezomib-based regimen, followed by maintenance, is a safe and effective treatment for elderly patients with multiple myeloma.

Bortezomib has also been investigated as an agent to improve clinical response in the postallogeneic SCT setting. The preclinical hypothesis of this use involves this drug blocking the nuclear factor-κB pathway that has been reported to exhibit multiple affects that include enhanced myeloma cell proliferation, a role in the inflammatory response pathway, enhanced apoptosis of alloreactive T cells and to promote cytotoxic T lymphocyte–induced tumor cell death to thus improve the graft-vs-myeloma response. Bruno et al[36,53] treated 23 MM patients with relapsed disease postallograft with bortezomib alone in varying doses and schedules or in combination with corticosteroids. The ORR was 61% including 22% CR rate, median PFS of 6 months, 91% OS at median of 6 months after treatment with bortezomib with 7 still in ≥VGPR. Yet, no significant increase in graft-versus-host disease (GVHD) was reported. Kroger et al[37] examined the use of bortezomib after reduced-intensity conditioning allo-SCT in 18 patients who achieved at least SD. Bortezomib 1.3 mg/m^2 IV was administered on days 1, 4, 8, and 11 every 21 days for 2 cycles at a median of 8 months after allo-SCT. Ten patients had measurable disease at the time of bortezomib administration, and 3 patients achieved CR, 5 patients achieved PR, and 2 patients had an magnetic resonance imaging. There was a significant increase of neuropathy in patients also on cyclosporine: 3 patients had a mild aggravation of skin GVHD, and 1 patient developed grade I acute GVHD. It is noteworthy that 2 other studies done showed improvement in patients who had myeloma relapse after allo-SCT and had chronic GVHD.[54] Follow-up study from Kröger et al demonstrated efficacy in the combination of bortezomib (in 8 of 32 patients) along with other agents (thalidomide and lenalidomide) in conjunction with donor lymphocyte infusion. This approach increased responses from PR to CR and significantly improved 5-year PFS.

MAINTENANCE THERAPY

Several studies have demonstrated its efficacy as frontline therapy and in relapsed, advanced MM, but results as MT in refractory/relapsed MM are less abundant.[54] The combination bortezomib/dexamethasone can be safely administered as an MT in relapse/refractory MM. These preliminary data suggest that bortezomib/dexametasone MT combinations improve remission duration with acceptable toxicity. In newly diagnosed MM, the combination of VMP was superior to MP.[51] In relapsed/refractory MM patients, the 4 drug combination bortezomib-melphalan-prednisone-thalidomide (VMPT) induced a relatively high proportion of CRs. The study was a prospective, randomized, phase III trial, compared VMPT with a maintenance regimen including bortezomib and thalidomide with VMP without a maintenance regimen and PFS as the primary end point. Weekly infusion of bortezomib reduced the incidence of peripheral neuropathy without affecting outcome with VMPT followed by maintenance with bortezomib and thalidomide superior to VMP for RRs and PFS. This was the first report to show the superiority of a 4-drug combination followed by maintenance.

CONCLUSIONS

In the field of cancer biology, the clinical success of the proteasome inhibitor bortezomib rapidly propelled the hematologic malignancy MM to a position of prominence as an efficient, validated preclinical model system to identify genetic lesions that contribute to disease, to unravel the pathways that contribute to oncogenesis and to test the therapeutic efficacy of novel compounds. Moreover, the availability of abundant, highly purified tumor

samples from newly diagnosed, untreated patients has provided a platform for gene expression profiling to further identify genes deregulated during myelomagenesis in both selected and selected patient populations and has further accelerated the ascent of the MM field to the forefront of the cancer biology arena.[55–57] Several therapeutic agents, such as the next generation proteasome inhibitors, now in clinical development were initially tested in myeloma systems. Seminal contributions from the basic biology and preclinical areas, such as linking the proteasome to the Ubiquitin-dependent proteolytic pathway, have translated into the clinical success of proteasome-based therapy in MM.[58,59]

The clinical success of bortezomib in the treatment of relapsed/refractory and newly diagnosed MM has led to novel combinations and applications as monotherapy, induction and MT. These therapies will be further refined to maximize benefit with minimal toxicity. Moreover, clinical trials with bortezomib as monotherapy have provided a basis for novel combinations such as combination chemotherapy regimen using lenalidomide, bortezomib, and dexamethasone in newly diagnosed myeloma patients.[44] An unprecedented 100% of patients treated at the defined phase 2 dose level responded to treatment: 74% of patients experienced a 90% reduction in tumor burden and 57% entered a CR within a few months of starting treatment. As noted, by Stewart,[60] there is little doubt that lenalidomide, bortezomib, and dexamethasone represents a step forward in myeloma care and serves as an important platform on which to build. Emerging proteasome inhibitors such as carfilzomib, NPI-0024, MLN9708, and CEP-18770, may demonstrate efficacy in additional malignancies and may overcome resistance to bortezomib that inevitably develops through unidentified means.

In recent years, it has become increasingly apparent that deregulation of the Ubiquitin + proteasome pathway contributes to the development of many forms of human cancer.[61] Ubiquitin and many ubiquitin-like modifiers, for example, Small Ubiquitin-like MOdifier (SUMO) and NEDD8, are crucial signals that control many biological processes and function in pathologies to represent an important class of targets for human therapeutics. Current efforts are focused on understanding how these ubiquitin-linked pathways participate in the etiology of different tumor types.[62–65] The SUMOylation pathway has been shown to be induced during myelomagenesis, to promote myeloma cell growth and proliferation and drug-resistance. Moreover, a gene signature comprising SUMO + Ub + Proteasome pathway components has been identified in patients with MM to predict response to bortezomib-based therapy. Targeting components of the Ubiquitin-like SUMOylation and NEDDylation pathways in malignancies may lead to promising tools as forms of cancer therapy.

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Table 1

Selected bortezomib regimens in treatment of MM

Reference	FDA/NCCN	Patient population	Patients	Regimen	Best response	Survival data
Jagannath et al[26]	N/Y – (Cat 1)	Previously untreated	32	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 6–3 wk cycles	88% ORR	OS 1 yr—87%
				Dex (40 mg/d of/after) for ≤PR after 2 cycles; ≤CR after 4 cycles	25% CR/nCR	
Harousseau et al[27]	N/Y – (Cat 1)	Previously untreated	48	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 4–3 wk cycles	66% ORR	NR
				Dex 40 mg on D1–4, 9–12 on C1 & 2; D1–4 on C3 & 4	21% CR	
				Consolidation to auto-SCT	10% VGPR	
Rosinõl et al[28]	N/Y – (Cat 1)	Previously untreated	40	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 6–3 wk cycles	77.5% ORR	NR
				Dex 40 mg on D1–4, 9–12, 17–20 on C2, 4, & 6	12.5% CR	
				Consolidation to auto-SCT	7.5% VGPR	
Richardson et al[29]	N/N	Previously untreated	64	Bor 1.3 mg/m^2 on D1, 4, 8, & 11	63% ORR	Med PFS—17 mos
				Max 8–3 wk cycles or 2 cycles past CR	9% CR/nCR	OS 2.5 yrs—79%
					8% VGPR	
Dispenzieri et al[22]	N/N	Previously untreated	39	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 8–3 wk cycles	51% ORR	PFS 2 yrs—16%
		High risk per protocol		Maintenance D1, 15 of 28 d cycle	0% CR	OS 2 yrs—76%
				Reinduction at PD	10% VGPR	
Popat et al[30]	Y/Y – (Cat 1)	Previously untreated	41	PAD1 (phase I)	62% ≥VGPR	PFS—29 v 24 mos
		–Induction regimen		Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 4–3 wk cycles	42% ≥VGPR	OS 1 yr−100% v 95%
		–Phase I/II		Doxo 0, 4.5, 9 mg/m^2 on D1–4 to max admin dose	(PAD1 v 2 – induction)	
				Dex 40 mg on D1–4, 8–11, 15–18—C1, D1–4—C2–4 PAD2 (phase II)		
				Bor 1 mg/m^2 on D1, 4, 8, & 11 for 4–3 wk cycles	81% ≥VGPR	OS 2 yrs
				Doxo 9 mg/m^2 on D1–4	53% ≥VGPR	−95% v 73%
				Dex 40 mg D1–4, 8–11, 15–18—C1, D1–4—C2–4	(PAD1 v 2 – posttransplant)	
				Consolidation w/auto-SCT		
Cavo et al[31]	N/Y – (Cat 1)	Previously untreated	474	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 3–3 wk cycles	19% CR *	PFS 2 yrs—85% *
		Induction regimen		Thal 200 mg/d on D1–63	62% ≥ VGPR *	OS 20 mos—93%
		Phase III trial		Dex 40 mg D1, 2, 4, 5, 8, 9, 11, 12	Postinduction	

Reference	FDA/NCCN	Patient population	Patients	Regimen	Best response	Survival data
				Consolidation w/auto-SCT × 2→ VTD × 2- 35 d cycle	44% CR *	
				Compared to TD→ auto-SCT × 2→ TD × 2- 35 d cycle	80% ≥ VGPR *	
					Full treatment	
Palumbo et al[32]	N/N	Previously untreated	102	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 4– 3 wk cycles	13% CR	PFS 2 yrs—69%
		Induction regimen		PLD 30 mg/m^2 on D4	58% ≥VGPR	OS 2 yrs—86%
		Phase II		Dex 40 mg D1–4, 8–11, 15–18—C1, D1–4—C2–4	Postinduction	
				Consolidation w/tandem auto-SCT w/MEL100	38% CR	
				Followed by Len/Pred→ maintenance Len	82% ≥VGPR	
					Posttransplant	
Moreau et al[33]	N/N	Previously untreated	205	Bor 1 mg/m^2 on D1, 4, 8, & 11 for 4–3 wk cycles	31% CR/nCR	NR
		Induction regimen		Thal 100 mg/d on D1–21	50% ≥ VGPR *	
		Phase III trial		Dex 40 mg D1–4, 8–11	Postinduction	
				Consolidation w/auto-SCT	60% CR/nCR	
				Compared to standard VTD regimen above	66% ≥ VGPR *	
					Post 1st ASCT	
Roussel et al[34]	N/N	Nonprogressive MM after induction	53	Bor 1 mg/m^2 on D-6, −3, +1, +4	32% CR	Median PFS-NR
		Conditioning reg.		MEL200 on D-2	70% ≥VGPR	PFS 2 yrs—76%
		Phase II trial		Auto-SCT reinfusion on D0	Posttransplant	
Harousseau et al[35]	N/Y – (Cat 1)	Previously untreated	482	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 4–3 wk cycles	15% CR/nCR *	PFS—36 mos
		Induction regimen		Dex 40 mg D1–4, 9–12 on C1 & 2; D1–4 on C3 & 4	38% ≥ VGPR *	OS 3 yrs—81%
		Phase III trial		Consolidation w/auto-SCT ± DCEP	79% ORR *	
				Compared to VAD induction	Postinduction	
					35% CR/nCR *	
					54% ≥ VGPR *	
					Post 1st ASCT	
Bruno et al[36]	N/N	Relapse s/p AlloSCT	23	Bor 1–1.3 mg/m^2 on D1, 4, 8, & 11 4-wk cycles	61% ORR	PFS—6 mos
		Retrospective		±Dex 20–40 mg on D1, 4, 15, and 18	22% CR	OS 6 mos—91%
Kröger et al[37]	N/N	Post-allo-SCT	18	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 2–3 wk cycles	30% CR	NR

Reference	FDA/NCCN	Patient population	Patients	Regimen	Best response	Survival data
		Enhance/maintain remission			50% PR	
					20% Min Res (10 patients w/residual dz)	
Kröger et al[38]	N/N	Post-allo-SCT	8	Bor 1.3 mg/m^2 on D1, 4, 8, & 11 for 4–3 wk cycles	59% CR	PFS 5 yrs—53%
		DLI + Bor/Thal/Len		Patients received median of 2 cycles (1–5)		OS 5 yrs—90%
						(no specific Bor data mentioned)
Sonneveld et al[39]	N/N	Maintenance	833	Bor 1.3 mg/m^2 every 2 wks for 2 yrs	CR 15→ 27%	NR
		Phase III trial		VAD v. PAD induction→ auto-SCT × 1–2→ Thal 50 mg/d (VAD arm) vs. Bor (PAD arm)		
Rosinõl et al[40]	N/N	Maintenance	390	Bor/Thal Maintenance for planned 3 yrs	NR	NR
				No doses noted in literature/clinical trials.gov		
				Compared to Thal alone and IFN		
Palumbo et al[41]	N/N	Maintenance	511	Bor/Mel/Pred/Thal induction	Maintenance did not improve RR	NR
				Bor 1.3 mg/m^2 every 2 wks		
				Thal 50 mg/d		
Ladetto et al[42]	N/N	Consolidation/maintenance	40	Bor 1.6 mg/m^2 on D1, 8, 15, 22 for 4–5 wk cycles	CR 15→ 49%	PFS—60 mos
				Thal 50 mg/d→ 200 mg/d; increase weekly as tolerated	MR 3→ 18%	OS 3 yrs—89%
				Dex 20 mg D1–4, 8–11, 15–18		
Nair et al[25]	N/N	Maintenance	177	Bor 1 mg/m^2 on D1, 4, 8, & 11 monthly for 1 yr	NR	NR
				Bor 1 mg/m^2 weekly for 2 yrs		
				Combined with Len/Dex for planned all 3 yrs		
Kumar et al[43]	N/N	Maintenance	117	Bor 1.3 mg/m^2 on D1, 8, 15, & 22 for 4–42 d cycles	NR	NR
Richardson et al[44]	N/N	Maintenance	68	Bor on D1 & 8 every 3 wks	NR	NR
				Combined with Len/Dex		
				No duration noted in article		
Mateos et al[45]	N/N	Maintenance	260	Bor/Thal/Pred v Bor/Mel/Pred Induction	CR	NR
				Bor 1.3 mg/m^2 on D1, 4, 8, & 11—3-wk cycle	VP: 39%	
				Given every 3 mos for 3 yrs	VT: 44%	
				Plus either Pred/Thal		

* Statistically significant difference between control and treatment groups

DLI, donor lymphocyte infusion.