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REVIEW ARTICLE

Bortezomib in multiple myeloma: systematic review and clinical considerations

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ABSTRACT

We conducted a systematic review to determine the appropriate use of bortezomib alone or in combination with other agents in patients with multiple myeloma (MM). We searched MEDLINE, EMBASE, the Cochrane Library, conference proceedings, and the reference lists of included studies. We analyzed randomized controlled trials and systematic reviews if they involved adult MM patients treated with bortezomib and if they reported on survival, disease control, response, quality of life, or adverse effects.

Twenty-six unique studies met the inclusion criteria. For patients with previously untreated MM and for candidates for transplantation, we found a statistically significant benefit in time to progression [hazard ratio (HR): 0.48, $p < 0.001$; and HR: 0.63, $p = 0.006$, respectively] and a better response with a bortezomib than with a non-bortezomib regimen ($p < 0.001$). Progression-free survival was longer with bortezomib and thalidomide than with thalidomide alone ($p = 0.01$). In non-candidates for transplantation, a significant benefit in overall survival was observed with a bortezomib regimen (HR compared with a non-bortezomib regimen: 0.61; $p = 0.008$), and in transplantation candidates receiving bortezomib, the response rate was improved after induction ($p = 0.004$) and after a first transplant ($p = 0.016$).

In relapsed or refractory MM, overall survival ($p = 0.03$), time to progression (HR: 1.82; $p = 0.000004$), and progression-free survival (HR: 1.69; $p = 0.000026$) were significantly improved with bortezomib and pegylated liposomal doxorubicin (compared with bortezomib alone), and bortezomib monotherapy was better than dexamethasone alone (HR: 0.77; $p = 0.027$). Bortezomib combined with thalidomide and dexamethasone was better than either bortezomib monotherapy or thalidomide with dexamethasone ($p < 0.001$).

In previously untreated or in relapsed or refractory MM patients, bortezomib-based therapy has improved disease control and, in some patients, overall survival.

KEY WORDS

Bortezomib, multiple myeloma, proteasome inhibitors, systematic review

1. INTRODUCTION

Bortezomib (Velcade: Millennium Pharmaceuticals, Cambridge, MA, U.S.A.), a first-in-class proteasome inhibitor, has been extensively studied either alone or in combination with other agents for the treatment of multiple myeloma (MM). Bortezomib works in the ubiquitin–proteasome pathway of cellular protein homeostasis by blocking the action of the 26S proteasome, a multicatalytic enzyme that degrades abnormal or misfolded proteins targeted for destruction, particularly those involved in cell cycling and gene transcription. Because those proteins are more abundant during the processes of carcinogenesis, they are key in cancer survival; proteasome inhibition in cancer cells leads to cell apoptosis and is, therefore, a target for therapy[1].

In 2008, bortezomib was approved by Health Canada for use as a first-line treatment for MM patients who are not candidates for stem-cell transplantation[2]. Existing consensus-based[3,4] and evidence-based[5,6] guidelines recommend the use of bortezomib for primary induction therapy in candidates and non-candidates for transplantation, and also for consolidation and salvage therapy after relapse.

Given that new data have recently become available, the Hematology Disease Site Group (DSG) at Cancer Care Ontario, in collaboration with the Program in Evidence-Based Care, conducted a systematic review to determine the appropriate use of bortezomib in patients with MM. This review constitutes the evidentiary basis of an updated Cancer Care Ontario guideline on bortezomib for MM and lymphoma (available at https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34323).

The systematic review addresses these questions:

- In patients with MM, what is the efficacy of bortezomib alone or in combination, as measured by survival, quality of life (QOL), disease control [for example, time to progression (TTP)], response duration, or response rate?
- What is the toxicity associated with the use of bortezomib?
- Which patients are more or less likely to benefit from treatment with bortezomib?

2. METHODS

2.1 Search Strategy

A search of the MEDLINE [Ovid (October 2004 through August 2012)], EMBASE [Ovid (2004 week 42 through August 27, 2012], and Cochrane Library (August 2012) databases used the key words "bortezomib," "bortezomid," "velcade," "ps?341," "ldp?341," and "mln?341" combined with key words specific to MM and with search strings identifying randomized controlled trials (RCTS), systematic reviews, and practice guidelines. In addition, conference proceedings of the American Society of Clinical Oncology (2005–2012) and the American Society of Hematology (2005–2011) and reference lists from the selected sources were searched for relevant trials. The Canadian Medical Association Infobase (http://www.cma.ca/index.php/ci_id/54316/la_id/1.htm), the U.S. National Guideline Clearinghouse (http://www.guideline.gov/), and the U.K. National Institute for Health and Care Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

2.2 Study Selection

Articles were selected for inclusion in this systematic review if they were published full-report articles or meeting abstracts of

- randomized studies including adult patients with MM and evaluating bortezomib as a single agent or in combination with other regimens.
- systematic reviews (full-report articles only), meta-analyses, or evidence-based clinical practice guidelines of bortezomib in adult patients with MM.

Trials could compare bortezomib with any agent, any combination of agents, or placebo, and could report results on any one or a combination of survival, QOL, disease control (for example, TTP), response duration, response rate, and adverse effects.

Articles were excluded if they were clinical practice guidelines without a description of a systematic literature search, abstracts of noncomparative studies, abstract reports of interim analyses, or systematic reviews that were more than 2 years old. Letters, comments, books, news, editorials, or abstract publications of systematic reviews were also excluded, as were articles published in a language other than English.

The methodologist (AEH or FGB) screened the titles and abstracts of the citations identified in the electronic databases and the titles of the abstracts from conference proceedings and excluded reports of studies that did not investigate the use of bortezomib or that did not meet the inclusion criteria for design (that is, they were not randomized trials or systematic reviews for MM). The full text of each remaining article was retrieved, and two authors (AEH or FGB and DER or TCK) reviewed the articles against the selection criteria.

For the evaluation of the quality of included RCTS, discrete parameters such as reporting of the sample-size calculation for the study, the randomization method, allocation concealment, blinding, intention-to-treat analysis, final analysis, early termination, losses to follow-up, and ethics approval were considered.

2.3 Data Analysis

Data appropriate for meta-analysis were not available because the heterogeneity of the studies did not allow for statistical pooling. A narrative synthesis is therefore presented, and the studies are grouped into untreated MM and into relapsed or refractory disease.

3. RESULTS

3.1 Literature Search

The literature search identified twenty-six unique studies: three guidelines based on systematic reviews[7–9], six systematic reviews[5,10–14], seventeen RCTS[15–31] and forty-seven related publications[32–78]. Figure 1 shows the study flow chart, and Table I presents the studies with their related publications and objectives.

Seven abstract publications of interim analyses of ongoing trials were also identified[79–85]. They are presented in Table I, but are not further discussed here.

The publications related to the main studies contributed information about extended follow-up of the original studies[33,45,49,53], subgroup analyses[34,39–44,48,51,52,55,57,59], health-related QOL[36,47,56,76], outcome data that were not reported in the original publication[35,37,46,49,54,60,61,64,68,74,78], and data on toxicity[38,50,62].

3.2 Trial Quality

Two trials reported in abstract form were randomized noncomparative phase II trials[18,65]. Because the authors of those trials did not compare the treatment

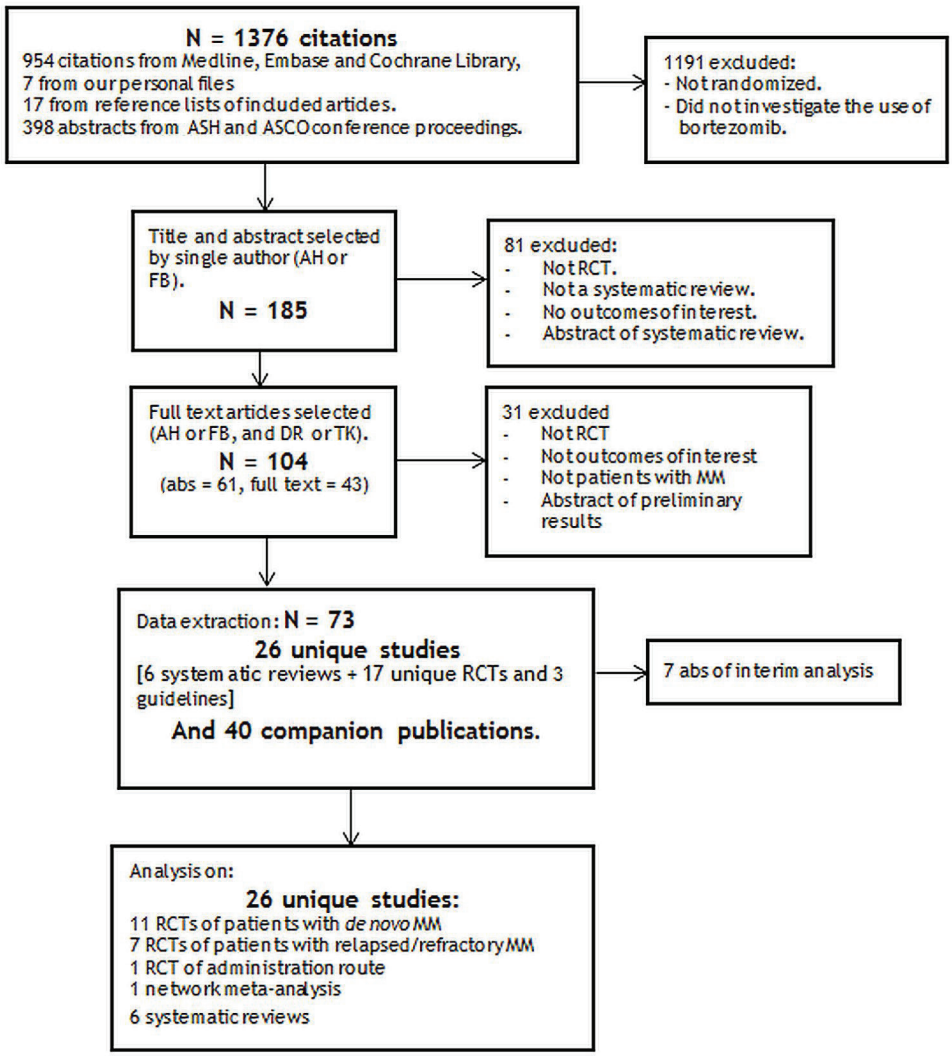

FIGURE 1 Systematic review on bortezomib for multiple myeloma (MM): study flow chart. ASH = American Society of Hematology; ASCO = American Society of Clinical Oncology; RCT = randomized controlled trial; abs = abstract.

arms within each trial on any outcome, neither trial is further discussed here.

We applied the AMSTAR tool[86,87] to measure the quality of the two systematic reviews (see Appendix 2, Table 2, in the Cancer Care Ontario Evidence-Based Series #6-18, available at https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34323).

Table II shows the quality assessment of the remaining RCTs.

Nine studies were available as fully published reports[15–17,19–24]. Eight of the nine fully published RCTs reported the *a priori* sample size required to find a statistically significant difference in the primary endpoints: TTP, progression-free survival (PFS), complete response (CR), pharmacokinetics and pharmacodynamics, and response rate[15,16,19–24]. Eight of the nine studies presented a final analysis[15–17,20–24], and seven of the eight conducted an intention-to-treat analysis[15,16,19–21,23,24]. Three studies were terminated early because the intervention significantly improved TTP[20,23,24]. One study conducted a blinded outcomes assessment[16], and three studies reported concealment of allocation[15,16,19]. None of the studies reported a loss to follow up exceeding 8%. The included studies were funded by pharmaceutical companies[15,16,23,24], government or philanthropic organizations[15,17,19,20], or by a foundation[21].

Among the studies reported in abstract form, one study stated that the analysis was final[63]. The other five[69,70,73,75,79] were identified as interim; they are not shown in Table II and will not be discussed further.

3.3 Study Characteristics

3.3.1 Previously Untreated MM

Indirect Comparison: The network meta-analysis by Kumar *et al.*[10] indirectly compared bortezomib

TABLE I Primary and additional publications of identified randomized trials of bortezomib in multiple myeloma

Study	*Primary publication and objective*	*Additional publications and objectives (when available)*
Fully published trials		
APEX	Richardson *et al.*, 2005[23]	
	Efficacy: bortezomib compared with high-dose dexamethasone in relapsed disease	
		Richardson *et al.*, 2007[32] — Update of APEX results
		Richardson *et al.*, 2007[33] — Extended follow-up
		San-Miguel *et al.*, 2008[34] — Subgroup analysis of patients with renal impairment
		Chanan–Khan *et al.*, 2008[35] — Herpes zoster events in bortezomib-treated patients
		Lee *et al.*, 2008[36] — Health-related QOL analysis
		Niesvizky *et al.*, 2008[37] — Response and clinical benefit in bortezomib-treated patients
		Richardson *et al.*, 2009[38] — Reversibility of peripheral neuropathy in bortezomib-treated patients
		Vogl *et al.*, 2009[39] — Prior exposure to specific therapies
		San Miguel *et al.*, 2011[40] (abs.) — Analysis of four phase III studies: APEX, MMY300, VISTA, and HOVON65 to assess the risk of second primary malignancies after bortezomib treatment
		Kaura and Dranitsaris, 2012[78] (abs.) — Compare the number needed to treat as a measure of drug benefit from data in the APEX study and a study of lenalidomide[50]
MMY-3001	Orlowski *et al.*, 2007[20]	
	Efficacy and safety: pegylated liposomal doxorubicin plus bortezomib compared with bortezomib monotherapy in relapsed or refractory disease	
		Sonneveld *et al.*, 2008[41] — Subgroup analysis of patients who received prior thalidomide or lenalidomide
		Shah *et al.*, 2008[42] (abs.) — Subgroup analysis of patients with paraprotein heavy- and light-chain types
		Shah *et al.*, 2008[43] (abs.) — Subgroup analysis of patients with bone marrow involvement
		Buda *et al.*, 2009[44] (abs.) — Investigate association between gene polymorphisms and response
VISTA	San Miguel *et al.*, 2008[24]	
	Efficacy: melphalan–prednisone compared with melphalan–prednisone–bortezomib in previously untreated disease	
		San Miguel *et al.*, 2008[45] (abs.) — Updated follow-up and results of subsequent therapy
		Harousseau *et al.*, 2008[46] — Assess the prognostic impact of response on time-to-event parameters
		Dhawan *et al.*, 2009[47] (abs.) — Health-related QOL
		Dimopoulos *et al.*, 2009[48] — Subgroup of patients with renal impairment
		Mateos *et al.*, 2010[49] — Confirm OS for melphalan–prednisone–bortezomib compared with melphalan–prednisone. Explore whether melphalan–prednisone–bortezomib induces relapses that are more resistant, and whether melphalan–prednisone–bortezomib used upfront was more effective than melphalan–prednisone
		Dimopoulos *et al.*, 2011[50] — Frequency, characteristics, reversibility, and potential risk factors of peripheral neuropathy
		Favis *et al.*, 2011[51] — Genetic variation associated with bortezomib-induced peripheral neuropathy

TABLE I Continued

Study	*Primary publication and objective*	*Additional publications and objectives (when available)*
	Delforge *et al.,* 2011[52]	Effects of bortezomib on bone events, remodelling, and healing
	San Miguel *et al.,* 2011[53] (abs.)	5-Year follow-up data
Ludwig	Ludwig *et al.,* 2009[18] (abs.)	
	Efficacy and toxicity: bortezomib–thalidomide–dexamethasone compared with bortezomib–thalidomide–dexamethasone plus cyclophosphamide in previously untreated patients	
GIMEMA	Cavo *et al.,* 2010[15]	
	Effectiveness: bortezomib–thalidomide–dexamethasone compared with thalidomide–dexamethasone as front-line therapy	
	Cavo *et al.,* 2009[58] (abs.)	Preliminary publication
	Brioli *et al.,* 2011[59] (abs.)	Impact of novel agents on peripheral stem-cell collection
	Cavo *et al.,* 2011[60] (abs.)	Per-protocol analysis of 321 patients who received the entire treatment program
	Cavo *et al.,* 2012[61]	Efficacy and safety: bortezomib–thalidomide–dexamethasone compared with thalidomide–dexamethasone as consolidation therapy after ASCT in newly diagnosed disease
	Tacchetti *et al.,* 2011[62] (abs.)	Analysis of bortezomib- and thalidomide-induced peripheral neuropathy
IFM 2005/01	Harousseau *et al.,* 2010[16]	
	Induction: bortezomib–dexamethasone compared with vincristine–doxorubicin–dexamethasone before ASCT	
	Avet–l'Oiseau *et al.,* 2010[55]	Effectiveness in overcoming the poor prognosis linked to translocation t(4;14)(p16;q32) in elderly patients
	Moreau *et al.,* 2010[56]	Evaluate stem-cell collection in the dexamethasone arm
	Moreau *et al.,* 2011[57]	Achievement of very good partial response at induction as a prognostic factor for longer PFS
Lonial	Lonial *et al.,* 2010[17]	
	Evaluate the safety and efficacy of combining bortezomib with high dose melphalan and the conditioning for high-dose therapy and ASCT	
Mateos, Spanish Myeloma Group, GEM2005MAS65	Mateos *et al.,* 2010[19]	
	Compare bortezomib–melphalan–prednisone plus maintenance with bortezomib–thalidomide–prednisone plus maintenance to investigate a bortezomib-based regimen that is less intensive than the regimen used in VISTA to maintain efficacy and to reduce toxic effects	
	Mateos *et al.,* 2011[64] (abs.)	Phase II of the 2010 study; all arms were randomly assigned to maintenance with bortezomib–prednisone or bortezomib–thalidomide
Palumbo	Palumbo *et al.,* 2010[21]	
	Compare bortezomib–melphalan–prednisone–thalidomide plus maintenance with bortezomib–thalidomide with bortezomib–melphalan–prednisone and no maintenance in newly diagnosed patients	
	Bringhen *et al.,* 2010[54]	Assess the impact of schedule change on clinical outcomes and safety

TABLE I Continued

Study	*Primary publication and objective*	*Additional publications and objectives (when available)*
IFM-2007–02	Moreau *et al.,* 2011[28]	
	Bortezomib–dexamethasone compared with reduced-dose bortezomib–thalidomide–dexamethasone before ASCT in newly diagnosed disease	
		Moreau *et al.,* 2010[69] (abs.) — Prior abstract publication of main study
Moreau, MMY-3021	Moreau *et al.,* 2011[29]	
	E efficacy and safety: subcutaneous compared with intravenous administration of bortezomib	
		Moreau *et al.,* 2011[68] (abs.) — Pharmacokinetics and pharmacodynamics of subcutaneous compared with intravenous administration of bortezomib
Reece	Reece *et al.,* 2011[22]	
	Pharmacokinetics and pharmacodynamics of bortezomib	
MMVAR/ IFM 2005–04	Garderet *et al.,* 2012[30]	
	Efficacy and safety: triple combination (bortezomib–thalidomide–dexamethasone) compared with dual combination (thalidomide–dexamethasone) in disease progressing or relapsing after ASCT	
Hjorth	Hjorth *et al.,* 2012[25]	
	Low-dose thalidomide–dexamethasone compared with bortezomib–dexamethasone in melphalan-refractory disease	
EVOLUTION	Kumar *et al.,* 2012[26]	
	Evaluate safety and efficacy of bortezomib–dexamethasone–lenalidomide, bortezomib–dexamethasone–cyclophosphamide, and bortezomib–dexamethasone–cyclophosphamide–lenalidomide in newly diagnosed patients	
		Kumar *et al.,* 2009[65] — Abstract report of main study
		Kumar *et al.,* 2011[66] — Abstract report of main study
		Kumar *et al.,* 2011[67] — Minimal residual disease assessment with multiparameter flow cytometry
Sharma	Sharma *et al.,* 2012[27]	
	Determine the efficacy and safety of adding bortezomib to a preparative regimen of arsenic trioxide, ascorbic acid, and melphalan in newly diagnosed patients	
		Sharma *et al.,* 2009[63] (abs.) — Previous publication
HOVON-65/ GMMG-HD4	Sonneveld *et al.,* 2012[31]	
	Induction: vincristine–doxorubicin–dexamethasone compared with bortezomib–doxorubicin–dexamethasone plus high dose melphalan and ASCT; maintenance: thalidomide compared with bortezomib in newly diagnosed disease	
		Sonneveld *et al.,* 2008[70] (abs.) — Abstract of interim analysis
		Neben *et al.,* 2012[71] — Prognostic value of 12 chromosomal abnormalities

TABLE I Continued

Study	*Primary publication and objective*	*Additional publications and objectives (when available)*
Abstracts of interim analyses		
Mellqvist	Mellqvist *et al.,* 2009[79] (abs.) Explore the effect of a 21-week consolidation period of single-agent bortezomib given during months 3–8 after ASCT	Mellqvist *et al.,* 2011[72] (abs.) Updated results
Vantage 088	Dimopoulos *et al.,* 2011[80] (abs.). Efficacy and safety: bortezomib plus vorinostat compared with bortezomib plus placebo in relapsed or refractory disease	
Dimopoulos	Dimopoulos *et al.,* 2011[81] (abs.) Efficacy: bortezomib–dexamethasone compared with bortezomib–dexamethasone–cyclophosphamide as second-line treatment	
UPFRONT	Niesvizky *et al.,* 2011[82] (abs.) Safety and efficacy: bortezomib–thalidomide–dexamethasone compared with bortezomib–dexamethasone and with bortezomib–melphalan–prednisone in newly diagnosed elderly patients	Niesvizky *et al.,* 2009[75] (abs.) Interim analysis Niesvizky *et al.,* 2011[76] (abs.) Patient-reported QOL
Orlowski	Orlowski *et al.,* 2012[83] (abs.) Efficacy and safety: siltuximab plus bortezomib compared with bortezomib plus placebo in relapsed or refractory disease	
PETHEMA/GEM 05	Rosinol *et al.,* 2012[84] (abs.) Effectiveness: thalidomide–dexamethasone compared with bortezomib–thalidomide–dexamethasone and with VBMCP/VBAD/bortezomib in newly diagnosed disease; presents data on time to progression	Rosinol *et al.,* 2009[73] (abs.) Interim analysis Rosinol *et al.,* 2011[74] (abs.) Data on response rate and time to progression
PANORAMA 1	San Miguel *et al.,* 2012[85] (abs.) Reports a blinded safety analysis from a randomized controlled trial: panobinostat plus bortezomib and dexamethasone compared with placebo plus bortezomib and dexamethasone in relapsed or refractory disease	San-Miguel *et al.,* 2011[77] (abs.) Update on 273 patients
Systematic reviews		
Palumbo	Palumbo *et al.,* 2009[5] Systematic review of evidence for an update to a previous guideline for the management of multiple myeloma	
Palumbo	Palumbo and Rajkumar 2010[12] Review of novel agents and discussion of the role of ASCT	

TABLE I Continued

Study	*Primary publication and objective*	*Additional publications and objectives (when available)*
Kumar	Kumar *et al.,* 2011[10]	Indirect comparison of melphalan–prednisone–thalidomide and melphalan–prednisone–bortezomib
HTA	Picot *et al.,* 2011[11]	Review the clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma; includes a systematic review and an economic evaluation
Piro	Piro *et al.,* 2011[13]	Systematic review of bortezomib in patients with renal impairment
Wang	Wang *et al.,* 2012[14]	Systematic review and meta-analysis of randomized controlled trials of novel agents bortezomib, lenalidomide, and thalidomide in newly diagnosed disease before ASCT; subgroup analyses were conducted by type of new agent
Guidelines		
Bird	Bird *et al.,* 2011[8]	Guidelines for the diagnosis and management of multiple myeloma
NICE technology appraisal guidance 228	Doss *et al.,* 2011[9]	Guidelines for the use of bortezomib and thalidomide for first-line treatment of multiple myeloma
SIE, SIES, gitmo	Barosi *et al.,* 2012[7]	Guidelines on the use of thalidomide, bortezomib, and lenalidomide for multiple myeloma

QOL = quality of life; abs. = abstract; OS = overall survival; ASCT = autologous stem-cell transplantation; PFS = progression-free survival; VBMCP = vincristine (1.2 mg/m^2 intravenously day 1), carmustine (20 mg/m^2 intravenously day 1), melphalan 8 mg/m^2 orally days 1–4), cyclophosphamide (400 mg/m^2 intravenously day 1), prednisone (40 mg/m^2 orally days 1–7); VBAD = vincristine, carmustine, doxorubicin, and high-dose dexamethasone; NICE = U.K. National Institute for Health and Care Excellence.

TABLE II Quality characteristics of included randomized controlled trials of bortezomib in multiple myeloma

Reference	*Treatment*	*Primary outcome*	*Required sample size (80% power, α = 0.05)*	*Sample size (n)*	*Randomization method*	*Allocation concealment*	*Blinding*	*Analysis*		*Early termination*	*Ethics approval*
								ITT	*Final*		
Fully published trials											
Richardson *et al.*, 2005[23]	B vs. high-dose D	TTP	310 Per arm to detect a 30% difference	Int: 333 Control: 336	NR	NR	No	Yes	Yes	Yes[a]	Yes
Orlowski *et al.*, 2007[20]	B vs. peg-Dox plus B	TTP	460 Events to detect a HR of 1.3	Int: 322 Control: 324	NR	NR	No	Yes	Yes[b]	Yes[c]	Yes
San Miguel *et al.*, 2008[24]	B–M–P vs. M–P	TTP	340 Per arm to detect a 33% improvement	Int: 344 Control: 338	NR	NR	No	Yes	Yes	Yes[d]	Yes
Cavo *et al.*, 2010[15]	B–T–D vs. T–D	CR or near-CR	225 Per arm to provide 80% power to detect a significant increase in CR plus near-CR from 15% with T–D to 27% with B–T–D	Int: 236 Control: 238	Central	Yes	No	Yes	Yes	No	Yes
Harousseau *et al.*, 2010[16]	V–Dox–D vs. V–Dox–D plus D–C–E–Cis consolidation vs. B–D vs. B–D plus D–C–E–Cis consolidation	CR or near-CR	110 Per arm to detect a 10% difference after induction	Int_1: 121 $Control_1$: 121 Int_2: 121 $Control_2$: 119	Central	Yes	Yes[e]	Yes	Yes	No	Yes
Lonial *et al.*, 2010[17]	Escalating dose of B 24 hours before vs. after high-dose M	Maximum tolerated dose	NR	Int: 19 Control: 20	NR	No	No	No	Yes	No	Yes
Mateos *et al.*, 2010[19]	Stage 1: B–M–P vs. B–T–P Stage 2: maintenance B–P vs. B–T	RR at induction and maintenance	130 Per arm to detect a 15% difference in CR after induction	Stage 1 – Int: 130 Control: 130 Stage 2 – $Int_{B–T}$: 44 $Control_{B–T}$: 47 $Int_{B–P}$: 43 $Control_{B–P}$: 44	Central	Yes	No	Yes	No	No	Yes

TABLE II Continued

Reference	*Treatment*	*Primary outcome*	*Required sample size (80% power, α = 0.05)*	*Sample size (n)*	*Randomization method*	*Allocation concealment*	*Blinding*	*Analysis*		*Early termination*	*Ethics approval*
								ITT	*Final*		
Palumbo *et al.*, 2010[21]	B–M–P–T plus B–T maintenance vs. B–M–P	PFS	250 Per arm to detect a HR of ≤0.75	Int: 254 Control: 257	NR	NR	No	Yes	Yes	No[f]	Yes
Reece *et al.*, 2011[22]	B 1.0 mg/m^2 vs. B 1.3 mg/m^2	Pharmacokinetics, pharmacodynamics	40 to obtain 24 evaluable (12 per arm)	Int: 21 Control: 21	NR	NR	NR	NR	Yes	No	Yes
Moreau *et al.*, 2011[28]	B subcutaneously vs. B intravenously	Non-inferiority of ORR: (lower bound of the 95% CI for ORR subcutaneous) — (0.6 × ORR intravenous) had to be ≥0	216 Needed, assuming the ORR in both groups to be 35.5%, and a one-sided α of 0.025 and about 80% power	222	Yes	Yes	No	No for primary efficacy endpoint; yes for TTP, PFS, and 1-year OS	No	No	Yes
Moreau *et al.*, 2011[29]	B–D induction before ASCT vs. reduced-dose B–T, plus D	Post-induction CR	200 Needed to provide 80% power, α 5% (two-sided test) to detect an 18% difference in CR assuming a 7% difference with B–D	199	Yes	Yes	NR	NR	Yes	No	Yes
Garderet *et al.*, 2012[30]	B–T–D vs. T–D	TTP	Study was designed to provide 90% power to detect a HR of 0.67 at a one-sided significance level of 0.025	269	NR	NR	NR	Yes	Yes	Yes[g]	Yes

TABLE II Continued

Reference	*Treatment*	*Primary outcome*	*Required sample size (80% power, α = 0.05)*	*Sample size (n)*	*Randomization method*	*Allocation concealment*	*Blinding*	*Analysis*		*Early termination*	*Ethics approval*
								ITT	*Final*		
Hjorth *et al.,* 2012[25]	T–D vs. B–D	PFS	300 Needed to detect a 50% difference in median PFS between treatment arms with a power of 89% and an α of 5%	131	Yes	Yes	NR	Yes[h]	Yes	No	Yes
Kumar *et al.,* 2012[26]	B–C–D, plus C on day 15 after interim vs. B–D–L vs. B–D–C–L vs. plus B maintenance in previously untreated patients	CR plus very good PR	39 Per arm required, or a total of 117 at α = 0.15, power of 80%; null hypothesis CR plus very good PR = 30% and alternative hypothesis CR plus very good PR = 45%	140	Yes	NR	NR	Yes	Yes	No	NR
Sharma *et al.,* 2012[27]	ATO and ascorbic acid vs. ATO, ascorbic acid, M, and B 1 mg/m^2 vs. B 1.5 mg/m^2 vs. ATO, ascorbic acid, M	CR, death, time to grade 4 toxicity	NR	Control: 20 Control$_1$: 20 Int$_2$: 20	NR	NR	No	No	Yes	No	NR
Sonneveld *et al.,* 2012[31]	Induction before high-dose M and ASCT: V–Dox–D vs. B–Dox–D Maintenance: T vs. B	PFS	800 Patients or 356 events needed to detect a HR = 0.74 with a power of 80% and α = 0.049	827	Yes	Yes	NR	Yes	Yes	No	Yes
Abstracts											
Niesvizky *et al.,* 2011[82]	B–D vs. B–T–D vs. B–M–P plus weekly B maintenance	PFS	NR	502	NR	NR	NR	NR	No	No	NR

TABLE II Continued

Reference	*Treatment*	*Primary outcome*	*Required sample size (80% power, α = 0.05)*	*Sample size (n)*	*Randomization method*	*Allocation concealment*	*Blinding*	*Analysis*		*Early termination*	*Ethics approval*
								ITT	*Final*		
Rosinol *et al.*, 2012[84]	Induction before ASCT: T–D vs. B–T–D vs. VBMCP/VBAD/B Maintenance: T–B vs. T vs. alfa-2b-interferon	TTP	NR	266 (maintenance only)	NR	NR	NR	Yes	No	No	NR
Orlowski *et al.*, 2012[83]	Siltuximab plus B vs. placebo plus B	PFS	NR	286	NR	NR	NR	NR	No	No	NR

[a] Trial was terminated early on recommendation from Data and Safety Monitoring Board after a planned interim analysis demonstrated significantly improved TTP in the bortezomib arm compared with dexamethasone. The *a priori* sample size requirement was met, but follow-up ended at the early termination date, and all patients in the dexamethasone arm were offered bortezomib.

[b] Data on overall survival, a secondary outcome, will continue to be collected by the authors, and a final analysis of that outcome will be conducted when 80% of patients have died.

[c] Trial was terminated early on recommendation from Data and Safety Monitoring Board after a planned interim analysis at 230 events demonstrated significantly improved TTP in the pegylated liposomal doxorubicin plus bortezomib arm compared with the bortezomib-alone arm.

[d] Trial was terminated early on recommendation from Data and Safety Monitoring Board after a planned interim analysis demonstrated significantly improved TTP in the bortezomib plus melphalan–prednisone arm compared with the melphalan–prednisone arm.

[e] Blinded assessors of outcomes.

[f] After the first 139 patients, the protocol was amended to reduce the incidence of peripheral neuropathy; 5-week cycles of 1.3 mg/m^2 bortezomib were used instead of 6-week cycles.

[g] Trial stopped at the second interim analysis for B–T–D superiority over T–D after 134 events and a median follow-up of 24 months.

[h] Except time to response and response duration.

ITT = intention-to-treat; B = bortezomib; D = dexamethasone; TTP = time to progression; Int = intervention; NR = not reported; peg-Dox = pegylated liposomal doxorubicin; M = melphalan; P = prednisone; T = thalidomide; CR = complete response; V = vincristine; Dox = doxorubicin; C = cyclophosphamide; E = etoposide; Cis = cisplatinum; RR = relative risk; PFS = progression-free survival; HR = hazard ratio; ORR = objective response rate; CI = confidence interval; OS = overall survival; ASCT = autologous stem-cell transplantation; L = lenalidomide; PR = partial response; ATO = arsenic trioxide; VBMCP = vincristine (1.2 mg/m^2 intravenously day 1), carmustine (20 mg/m^2 intravenously day 1), melphalan 8 mg/m^2 orally days 1–4), cyclophosphamide (400 mg/m^2 intravenously day 1), prednisone (40 mg/m^2 orally days 1–7); VBAD = vincristine, carmustine, doxorubicin, and high-dose dexamethasone.

and thalidomide (both in combination with melphalan and prednisone) in newly diagnosed MM patients. No differences were detected for most outcomes, but benefits in CR [relative risk (RR): 2.34; 95% confidence interval (CI): 1.12 to 4.90] and in grade 3 or 4 adverse events (RR: 0.53; 95% CI: 0.38 to 0.73) were observed in favour of the bortezomib combination.

Direct Comparison: Eleven RCTs—nine full-text publications[15,16,19,21,24,26–28,31] and two abstracts[82,84]—examined the use of bortezomib in patients with *de novo* MM. Table III details inclusion criteria and intervention details for those trials.

Non-transplantation Therapy: Five trials enrolled newly diagnosed patients who were not candidates for autologous stem-cell transplantation (ASCT) either because of older age (≥65 years) or because of other coexisting conditions[19,21,24,26,82].

Transplantation Therapy: Six RCTs enrolled younger untreated MM patients who were candidates for ASCT[15,16,27,28,31,84].

3.3.2 Relapsed or Refractory MM

Seven RCTs examined the use of bortezomib in patients with relapsed or refractory MM. All studies but one were fully published reports. Three included only bortezomib-naïve patients[20,23,25]; the remaining four[17,22,30,83] included patients who had previously received treatment for MM, including bortezomib. Table IV details the characteristics of the study patients.

The primary outcomes in the studies of patients with relapsed or refractory MM were TTP[21,23,30], PFS[25,83], and toxicity[17]. Reece *et al.*[22] reported on pharmacodynamic and pharmacokinetic parameters, response, and the toxicity of bortezomib.

3.4 Endpoints

Question: What is the efficacy of bortezomib alone or in combination?

The subsections that follow summarize the results of the included trials. Detailed efficacy data can be found in Table V.

3.4.1 Previously Untreated MM

TTP: Among the studies of patients who were not candidates for ASCT, the VISTA study[24] found a significant difference in TTP after induction with bortezomib compared with a non-bortezomib-containing regimen (HR: 0.48; $p < 0.001$). The other studies either did not report results for this endpoint[21,26,82] or did not find a significant difference when comparing bortezomib in two different combination regimens[19]. None of the studies involving patients who were candidates for ASCT reported on this endpoint.

Overall Survival: Among studies of patients who were not candidates for ASCT, the VISTA trial[24,56,57] reported a statistically significant difference in overall survival (OS) when bortezomib was compared with a non-bortezomib-containing regimen (HR: 0.65; $p < 0.001$). In the studies of transplant patients, Sonneveld *et al.*[31] demonstrated a statistically significant difference in OS (HR: 0.77; 95% CI: 0.60 to 1.00; $p = 0.049$); in the other studies, median OS was not significantly different for the control groups or was not estimable (see Table V).

PFS: Among studies of patients who were not candidates for ASCT, Palumbo *et al.*[21] found a statistically significant difference in PFS favouring bortezomib in a 4-drug combination induction regimen plus bortezomib-containing maintenance compared with bortezomib in a 3-drug combination induction alone (HR: 0.67; $p = 0.008$). In a related abstract publication, Niesvitzky *et al.* found no significant difference in PFS between the treatment arms[82].

Among the studies of patients who were candidates for ASCT, Sonneveld *et al.*[31] found a significantly longer PFS in patients allocated to bortezomib, doxorubicin, and dexamethasone than in patients allocated to vincristine, doxorubicin, and dexamethasone (HR: 0.74; 95% CI: 0.62 to 0.89; $p < 0.001$). Cavo *et al.*[15] suggested a significantly better PFS, projected to be 36 months, for bortezomib, dexamethasone, and thalidomide compared with dexamethasone and thalidomide (HR: 0.63; 95% CI: 0.45 to 0.88; $p < 0.006$). Harousseau *et al.*[16] compared a bortezomib–dexamethasone combination with a vincristine–doxorubicin–dexamethasone combination, but PFS did not reach statistical significance in favour of the bortezomib arm ($p = 0.057$). In an abstract publication, Rosinol *et al.*[84] found that PFS was statistically significantly longer in the bortezomib–thalidomide arm than in the thalidomide-alone or interferon arms (PFS at 2 years: 78% vs. 63% vs. 49%; $p = 0.01$).

QOL: Health-related QOL was measured using various domains of the European Organisation for Research on Treatment of Cancer Quality of Life Questionnaire–Core (QLQ-C30)[88] in two studies[47,76]. In a subanalysis of the VISTA trial[24], Dhawan *et al.*[47] showed that newly diagnosed MM patients treated with bortezomib, melphalan, and prednisone had a higher sustained rate of improvement in health-related QOL than did patients treated with melphalan and prednisone (14 of 15 domains). They also reported a statistically significant improvement in 3 domains: Nausea/Vomiting ($p = 0.0095$), Appetite Loss ($p = 0.0170$), and Diarrhea ($p = 0.0082$)[47]. Niesvitsky *et al.*[76] found no statistically significant differences between arms.

Response Rate: In patients who were not candidates for ASCT, CR and overall response (OR) were found to be statistically significantly different for a bortezomib compared with a non-bortezomib-containing regimen (CR: 30% vs. 4%, $p < 0.001$; OR:

TABLE III Patient characteristics in studies of patients with *de novo* multiple myeloma

Reference	*Intervention*	*Patients*		*Median age (years)*
		Included	*Excluded*	
Non-ASCT trials				
San Miguel *et al.,* 2008[24]	Int: M–P–B Control: M–P	Newly diagnosed, previously untreated, ineligible for high-dose therapy plus SCT and had symptomatic, measurable disease	Patients who were not candidates for high-dose therapy plus ASCT because of age ≥65 years	71
Mateos *et al.,* 2010[19]	Int: B–T–P plus maintenance with B–P or B–T Control: B–M–P plus maintenance with B–P or B–T	65 Years of age or older with newly diagnosed, untreated, symptomatic, measurable disease	Patients with grade 2 or greater peripheral neuropathy, serum creatinine > 176.8 μmol/L, or ECOG performance status 3 or 4	73
Palumbo *et al.,* 2010[21]	Int: B–M–P–T plus B–T maintenance Control: B–M–P with no maintenance	Newly diagnosed, with measurable disease, Karnofsky performance status ≥60%, ineligible for high-dose therapy plus SCT because of age ≥65 years or comorbidities	Patients with renal insufficiency (creatinine ≥25 mg/L); uncontrolled or severe CVD, psychiatric disease, any grade 2 peripheral neuropathy, other malignancy within the past 5 years	71
Niesvizky *et al.,* 2011[82] (abs.)	Induction (eight 21-day cycles): B–D vs. B–T–D vs. B–M–P Maintenance: B	Symptomatic, measurable disease	NR	Int: 74.5 $Control_1$: 73 $Control_2$: 72
Kumar *et al.,* 2012[26]	Int: B–D–C–L $Control_1$: B–D–C $Control_2$: B–D–L $Control_3$: B–C–D with C on day 15	18 Years of age or older with previously untreated, symptomatic, measurable disease, regardless of eligibility for ASCT	Patients with MI in the past 6 months, heart failure, uncontrolled angina, or significant arrhythmia	61
ASCT trials				
Sharma *et al.,* 2012[27]	Int_1: low-dose B plus M, plus ATO, plus ascorbic acid plus ASCT Int_2: high-dose B plus M, plus ATO, plus ascorbic acid plus ASCT Control: M plus ATO, plus ascorbic acid, plus ASCT	Age less than 75 years, Zubrod performance status < 2, LVEF > 40% with no uncontrolled arrhythmia or unstable cardiac disease, a corrected AT interval < 470 ms, adequate pulmonary function, serum bilirubin < 2 times the ULN, and serum glutamic pyruvic transaminase < 4 times the ULN	HIV positivity, pregnancy	Int_1: 59 Int_2: 64 Control: 61

TABLE III Continued

Reference	*Intervention*	*Patients*		*Median age (years)*
		Included	*Excluded*	
Cavo *et al.,* 2010[15]	Int: B–T–D plus double ASCT Control: T–D plus double transplantation	Less than 65 years of age with newly diagnosed disease	Grade 2 or greater peripheral neuropathy; history of venous thromboembolism; previous diagnosis of thrombophilic alterations	Int: 58 Control: 57
Harousseau *et al.,* 2010[16]	Int_1: B–D and no consolidation Int_2: B–D plus D–C–E–P consolidation $Control_1$: V–Dox–D and no consolidation $Control_2$: V–Dox–D plus D–C–E–P consolidation	Less than 65 years of age with measurable disease; ECOG performance status of 2 or less; life expectancy of 2 months or more; and adequate renal, hematologic, and hepatic function	Confirmed amyloidosis, HIV positivity, history of other malignancy, uncontrolled diabetes, and grade 2 or greater peripheral neuropathy	Int: 57.2 Control: 57.1
Moreau *et al.,* 2011[28]	B–D vs. reduced-dose B–T plus D before ASCT	65 Years of age or less, with symptomatic and measurable disease, ECOG performance status ≤ 2, and adequate renal function	Confirmed amyloidosis, HIV positivity, history of other malignancy, uncontrolled diabetes, and grade 2 or greater peripheral neuropathy	Int: 57 Control: 58
Rosinol *et al.,* 2012[84] (abs.)	Maintenance: T–B vs. T vs. alfa-2b-interferon	Newly diagnosed symptomatic disease and ASCT	NR	NR
Sonneveld *et al.,* 2012[31]	Induction: B–Dox–D plus high-dose M, plus ASCT Maintenance: B 1.3 mg/m^2 every 2 weeks	18–65 Years of age with newly diagnosed disease stage II–III, WHO performance status 0–2 or 3 if caused by the multiple myeloma	Systemic amyloid chain amyloidosis, nonsecretory disease, neuropathy grade 2 or greater, active malignancy during the past 5 years, HIV positivity, serum aminotransferases ≥ 30 µmol/L or ≥ 2.5 times normal	57

ASCT = autologous stem-cell transplantation; Int = intervention group; M = melphalan; P = prednisone; B = bortezomib; SCT = stem-cell transplantation; T = thalidomide; ECOG = Eastern Cooperative Oncology Group; CVD = cardiovascular disease; abs. = abstract; D = dexamethasone; NR = not reported; L = lenalidomide; C = cyclophosphamide; MI = myocardial infarction; ATO = arsenic trioxide; LVEF = left ventricular ejection fraction; ULN = upper limit of normal; HIV = human immunodeficiency virus; C = cyclophosphamide; V = vincristine; Dox = doxorubicin.

TABLE IV Patient characteristics in studies of patients with relapsed or refractory multiple myeloma

Reference	*Intervention*	*Patients*		*Median age (years)*
		Included	*Excluded*	
Richardson *et al.,* 2005[23]	Int: B Control: High-dose D	Presence of measurable progressive disease after 1–3 previous treatments, Karnofsky performance status 60% or higher, platelet count of 50,000/mm^3 or higher, hemoglobin 7.5 g/dL or greater, ANC 750/mm^3 or higher, creatinine clearance 20 mL/min or greater	Previously received bortezomib; disease refractory to high-dose dexamethasone; peripheral neuropathy grade 2 or higher; significant coexisting illness	Int: 62 Control: 61
Orlowski *et al.,* 2007[20]	Int: B plus peg-Dox Control: B	Bortezomib-naïve, with confirmed and measureable disease progressing after 1 or more lines of therapy, or refractory to initial treatment; ECOG performance status 0–1; platelets 75,000/mm^3 or greater, hemoglobin 8 g/dL or greater, ANC 1000/mm^3 or greater, creatinine clearance 30 mL/min or greater	Previous progression while receiving anthracycline-containing therapy; prior exposure to doxorubicin exceeding 240 mg/m^2; cardiac disease, peripheral neuropathy grade 2 or greater	61
Lonial *et al.,* 2010[17]	Int: M plus 1 dose B 24 h before high-dose M Control: M plus 1 dose B 24 h after high-dose M	Measurable disease in bone marrow, and response less than very good PR after induction (3 patients previously treated with ASCT; 23 patients previously exposed to bortezomib)	NR	60
Reece *et al.,* 2011[22]	Int: B 1.3 mg/m^2 Control: B 1.0 mg/m^2	18 Years of age or older, with relapsed disease after 1 or more prior lines of therapy	Significant cardiac disease, active systemic infection, serious medical or psychiatric illness, grade 2 or greater neuropathy, active hepatitis, HIV disease, a secondary malignancy, plasma-cell leukemia, POEMS syndrome	61.5
Garderet *et al.,* 2012[30]	B–T–D vs. T–D	Measurable disease that progressed or relapsed once after ASCT, Karnofsky performance status exceeding 50%, platelets 40,000/μL or greater, ANC 1000 μL or greater, creatinine clearance 30 mL/min or greater	Previous allogeneic transplantation	61.2

TABLE IV Continued

Reference	Intervention	Patients		Median age (years)
		Included	Excluded	
Hjorth *et al.*, 2012[25]	B–D vs. T–D	Any age, with symptomatic disease refractory to melphalan	Previous treatment with thalidomide, bortezomib or lenalidomide; sensory neuropathy grade 3 or greater; platelet count less than 25×10^9/L; severe comorbidity; transformation to plasma-cell leukemia or aggressive lymphoma; nonsecreting disease without abnormal free light-chain ratio	71
Orlowski *et al.*, 2012[83] (abs.)	Siltuximab + B vs. placebo plus B	NR	NR	Int: 64 Control: 61

Int = intervention group; B = bortezomib; D = dexamethasone; ANC = absolute neutrophil count; peg-Dox = pegylated liposomal doxorubicin; ECOG = Eastern Cooperative Oncology Group; M = melphalan; PR = partial response; ASCT = autologous stem-cell transplantation; NR = not reported; POEMS = polyneuropathy, organomegaly, endocrinopathy, plasma-cell leukemia; T = thalidomide.

71% vs. 35%, $p < 0.001$)[24] and for a 4-drug–plus–maintenance combination compared with a 3-drug combination (CR: 38% vs. 24%, $p < 0.001$; OR: 59% vs. 50%, $p = 0.03$)[21]. No statistically significant difference was found when comparing two 3-drug combinations containing bortezomib[19].

Among patients who were candidates for transplantation, Harousseau *et al.*[16] found a statistically significant difference in CR in favour of a bortezomib–dexamethasone combination both after induction and after a first transplant (induction: 14.8% vs. 6.4%, $p = 0.004$; first transplant: 16.1% vs. 8.7%, $p = 0.016$). Sonneveld *et al.*[31] found a statistically significant difference in CR in favour of bortezomib at induction and at maintenance (7% vs. 2% and 21% vs. 9% respectively, $p < 0.001$). For OR after first transplant, no statistically significant difference was detected[16]. Cavo *et al.*[15] reported a significant difference in CR in favour of bortezomib–dexamethasone–thalidomide compared with thalidomide–dexamethasone at induction, after first transplantation, at second transplantation after consolidation, and overall (*p* values shown in Table IV). Moreau *et al.*[28] found no statistically significant difference in CR and objective response rate between study arms.

3.4.2 Relapsed and Refractory MM

TTP: Bortezomib monotherapy improved TTP statistically significantly more than did dexamethasone alone (HR: 0.55; $p < 0.001$)[23]. Compared with bortezomib monotherapy, the combination of bortezomib with pegylated liposomal doxorubicin (PLD) significantly improved TTP (HR: 1.82; $p = 0.000004$)[20]. As well, bortezomib–dexamethasone or bortezomib–thalidomide–dexamethasone were more effective than thalidomide–dexamethasone in improving TTP ($p < 0.005$ and $p < 0.001$, Table IV)[25,30].

OS: Bortezomib in combination with PLD was found to significantly improve OS (65% vs. 76%, $p = 0.03$)[20]. Bortezomib monotherapy improved OS significantly more than did dexamethasone (HR: 0.77, $p = 0.003$; and HR: 0.67, $p = 0.47$)[23,33]. No significant difference was seen with the administration of bortezomib before or after melphalan[17] or in combination with thalidomide, dexamethasone, or siltuximab[25,30,83].

PFS: Bortezomib in combination with PLD (compared with bortezomib alone) and bortezomib–thalidomide–dexamethasone (compared with thalidomide–dexamethasone) were found to significantly improve PFS (HR: 1.69, $p = 0.000026$, and HR: 0.61, $p < 0.001$, respectively)[20,30].

Response Rate: No significant difference in OR or CR was detected between bortezomib monotherapy and bortezomib plus PLD[20]. Bortezomib monotherapy was significantly better than dexamethasone for CR and OR ($p < 0.001$)[33]. Bortezomib in a 3-drug

TABLE V Results of studies of patients with multiple myeloma

Reference	*Intervention*	*PFS (months)*	*Median TTP (months)*	*OR (%)*	*CR (%)*	*Median OS (months)*	*Median follow-up (months)*
Previously untreated disease							
Non-ASCT trials							
San Miguel *et al.*, 2008[24]	Int: B–M–P	NR	24	71[a]	30[a]	NE	36.7/16.3[b]
	Control: M–P	NR	16.6 HR: 0.48 $p<0.001$[c]	35[a] $p<0.001$	4[a] $p<0.001$	43%[b] HR: 0.61 $p=0.008$	
Mateos *et al.*, 2010[19]	Induction: B–M–P[d]	NS	NS	NS[c]	NR	NS	32
	Induction: B–T–P	NS	NS	NS[c]	NR	NS	
	Maintenance: B–T	NS	NR	NR	NR	NS	
	Maintenance: B–P	NS	NR	NR	NR	NS	
Palumbo *et al.*, 2010[21]	Int: B–M–P–T plus B–T[d]	56%	NR	59	38	89%	23.2
	Control: B–M–P	41% HR: 0.67[c] $p=0.008$[c]	NR	50 $p=0.03$	24 $p<0.001$	87% HR: 0.92 $p=0.77$	
Niesvizky *et al.*, 2011[82] (abs.)	B–T	13.8	NR	73	30	87.4%	21.8
	B–T–D	14.7	NR	80	40	86.1%	
	B–M–P	17.3 (NS)	NR	69	33	88.9%	
Kumar *et al.*, 2012[26]	B–D–C–L	86	NR	88	25	100%	20
	B–D–L	83	NR	85	24[e]	100%	
	B–D–C	93	NR	75	22	100%	
	B–D–C with C on day 15	100	NR	100	47	100%	

TABLE V Continued

Reference	*Intervention*	*PFS (months)*	*Median TTP (months)*	*OR (%)*	*CR (%)*	*Median OS (months)*	*Median follow-up (months)*
ASCT trials							
Cavo *et al.*, 2010[15]	B–T–D → double ASCT → B–T–D consolidation	68% (estimated at 3 years)	29%	NR	After induction: 44[c] After 1st ASCT: 89 After 2nd ASCT: 98 After consolidation: 116 Overall treatment: 136 $p<0.0001$	NS[h]	36
	D–T → double ASCT → B–T–D consolidation	56% $p=0.0057$ HR: 0.63 (95% CI: 0.45 to 0.88, $p=0.0061$)	39% $p=0.0061$	NR	After induction: 11 After 1st ASCT: 54 ($p=0.0004$) After 2nd ASCT: 72 ($p=0.0105$) After consolidation: 82 ($p=0.0012$) Overall treatment: 97 $p=0.0001$	NS	
Harousseau *et al.*, 2010[16]	Int_1: B–D and no consolidation Int_2: B–D plus D–C–E-Cis consolidation → ASCT	36.0	NR	After induction: 78.5 $p<0.001$ After 1st transplant: NS	After induction: 14.8[c,f] $p=0.004$ After 1st transplant: 16.1 $p=0.016$	NE[g]	32.2
	$Control_1$: V–Dox–D and no consolidation $Control_2$: V–Dox–D plus D–C–E-Cis consolidation → ASCT	29.7 $p=0.057$	NR	After induction: 62.8	After induction: 6.4 After 1st transplant: 8.7	NE[d]	
Moreau *et al.*, 2011[28]	B–D	30	NR	36	13	45%	32
	Reduced-dose B–T plus D	26 (NS)	NR	49 $p=0.05$	12 (NS)	53% (NS)	

TABLE V Continued

Reference	*Intervention*	*PFS (months)*	*Median TTP (months)*	*OR (%)*	*CR (%)*	*Median OS (months)*	*Median follow-up (months)*
Rosinol *et al.,* 2012[84] (abs.)	Maintenance: B–T	78	NR	NR	23	NS	24
	Maintenance: T	63	NR	NR	11	NS	
	Maintenance: interferon	49 p=0.01	NR	NR	NS	NS	
Sharma *et al.,* 2012[27]	ASCT prep: M, ascorbic acid, ATO plus B 1.0 mg/m^2	17.8	NR	85	20[c]	NE[c]	36
	ASCT prep: M, ascorbic acid, ATO plus B 1.5 mg/m^2	17.4	NR	90	10[c]	NE[c]	
	ASCT prep: M, ascorbic acid, ATO	20.7	NR	95	10[c]	NE[c] p=0.057	
Sonneveld *et al.,* 2012[31]	Induction: B–Dox–D plus high-dose M, plus ASCT → Maintenance: B	35	NR	NR	7→21	61%	41
	Induction: V–Dox–D plus high-dose M, plus ASCT → Maintenance: T	28 (p<0.002)	NR	NR	2→9 p<0.001	55% p=0.049	
Relapsed or refractory disease							
Richardson *et al.,* 2005[23]	B	NR	6.2[c]	38	6	29.8[i]	22
	D	NR	3.5[c] HR: 0.55 p<0.001	18 p<0.001	1 p<0.001	23.7[i] HR: 0.77 p=0.027	
Orlowski *et al.,* 2007[20]	B	6.5	6.5[c]	41	2	65%	7.2[g]
	B plus peg-Dox	9.0 HR: 1.69 p=0.000026	9.3[c] HR: 1.82 (95% CI: 1.41 to 2.35) p=0.000004	44 p=0.43	4	76% (15 months) p=0.03	

TABLE V Continued

Reference	*Intervention*	*PFS (months)*	*Median TTP (months)*	*OR (%)*	*CR (%)*	*Median OS (months)*	*Median follow-up (months)*
Lonial *et al.,* 2010[17]	B (escalating doses of 1.0, 1.3, and 1.6 mg/m^2) 24 hours before M	NS	NR	47	11	NS	17.3
	B (escalating doses of 1, 1.3, and 1.6 mg/m^2) 24 hours after M	NS	NR	55	30	NS	
Reece *et al.,* 2011[22]	B 1.3 mg/m^2	NR	NR	52	5	NR	NR
	B 1.0 mg/m^2	NR	NR	48	10	NR	
Garderet *et al.,* 2012[30]	B–T–D	19.3	19.5	45	45	71%	30
	T–D	13.6	13.8	25	25	65%	
		$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$	(NS)	
Hjorth *et al.,* 2012[25]	B–D	7.2	1.6	63	NR	19	3.5 on B,
	T–D	9	3.0	55	NR	22.8	5.1 on T[j]
		(NS)	$p<0.005$	(NS)			
Orlowski *et al.,* 2012[83] (abs.)	Siltuximab plus B	8.1	NR	55	11	30.8	24.5
	B	7.6	NR	47	7	36.9	
		(NS)		(NS)	(NS)	(NS)	

[a] Results in evaluable population (B–M–P: $n = 337$; M–P: $n = 331$).
[b] Median follow-up was 36.7 months for overall survival and 16.3 months for time to progression in the original publication. An update[55] confirmed a statistically significant survival benefit for B–M–P compared with M–P at a median follow-up of 25.9 months (HR: 0.64; $p = 0.003$). In a further publication[59], 3-year rates of overall survival were estimated at 68.5% for B–M–P compared with 54% with M–P.
[c] Results for primary outcome.
[d] Bortezomib on a weekly schedule.
[e] The original data cut-off was April 28, 2006, at which time the median follow-up was 7.2 months; survival and time to event data were reanalyzed with a data cut-off of November 28, 2006, upon request by the U.S. Food and Drug Administration. Median follow-up for overall survival and time to progression were not reported.
[f] Results in the evaluable population (B–D: $n = 223$ after induction, $n = 197$ after first transplant; V–Dox–D: $n = 218$ after induction, $n = 184$ after first transplant).
[g] Median overall has not been reached in either group. Overall survival rates were 81.4% with B–D and 81.4% with V–Dox–D.
[h] The estimated 3-year overall survival was 86% compared with 84% ($p = 0.30$).
[i] Data from an additional publication[41].
[j] Terminated early because of low accrual.

PFS = progression-free survival; TTP = time to progression; OR = odds ratio; CR = complete response; OS = overall survival; ASCT = autologous stem-cell transplantation; Int = intervention group; B = bortezomib; M = melphalan; P = prednisone; NR = not reported; HR = hazard ratio; NE = not reached or not estimable; T = thalidomide; NS = statistically nonsignificant; D = dexamethasone; C = cyclophosphamide; L = lenalidomide; abs. = abstract; E = etoposide; Cis = cisplatinum; V = vincristine; Dox = doxorubicin; ATO = arsenic trioxide; peg-Dox = pegylated liposomal doxorubicin; CI = confidence interval.

TABLE VI Randomized trials of patients with multiple myeloma: adverse events

Reference	*Intervention*	*Pts (n)*	*Neutropenia (%)*[a]	*Thrombocytopenia (%)*[a]	*Anemia (%)*[a]	*Peripheral neuropathy (%)*[a]	*Infection (%)*[a]	*Adverse events leading to discontinuation (%)*	*Treatment-related death (%)*	*Serious adverse events (%)*
Previously untreated disease										
Non-ASCT trials										
San Miguel *et al.*, 2008[24]	B–M–P	340	40	37	19	13	7[b]	15	1	46
	M–P	337	38	30	28	0	5[b]	14[c]	2	36
		p=NS	p=NS	p=NS		p=NR	p=NS	p=NS	p=NS	p=NR
Mateos *et al.*, 2010[19]	Induction:									
	B–M–P	130	39	27	12	7	7	12	5[d]	15
	B–T–P	130	22	12	8	9	1	17	5	31
			p=0.008	p=0.0001	p=NS	p=NS	p=0.01	p=0.03	p=NS	p=0.01
	Maintenance:									
	B–T	91	2	1	4	7	2	8	1	NR
	B–P	87	1	1	3	2	2	5	1	NR
			p=NS	p=NS	p=NS	p=NS	p=NS	p=NS	p=NS	
Palumbo *et al.*, 2010[21]	B–M–P–T plus B–T	250	38	22	10	8	13	23	4	NR
	B–M–P	253	28	20	10	5	9	17	3	NR
			p=0.02	p=NS	p=NS	p=NS	p=NS	p=NS	p=NS	
Niesvizky *et al.*, 2011[82] (abs.)	B–D	146	NR	NR	NR	NR	NR	24[e]	5[e]	48[e]
	B–T–D	133	NR	NR	NR	NR	NR	35[e]	6[e]	53[e]
	B–M–P	144	NR	NR	NR	NR	NR	30[e]	5[e]	47[e]
Kumar *et al.*, 2012[26]	B–D–C–L	48	44	15	8	13	NR	21	2	NR
	B–D–L	42	10	112	7	17	NR	19	0	NR
	B–D–C	33	30	12	0	9	NR	12	0	NR
	B–C–D plus C on day 15	17	24	0	12	18	NR	6	0	nr
ASCT trials										
Sharma *et al.*, 2012[27]	ASCT prep:									
	ATO, ascorbic acid, M, B 1 mg/m^2	20	NR	NR	NR	0	5[b]	NR	5	NR
	ATO, ascorbic acid, M, B 1.5 mg/m^2	19	NR	NR	NR	0	0	NR	0	NR
	M, ascorbic acid, ATO	19	NR	NR	NR	0	0	NR	0	NR
						p=NS	p=NS		p=NS	

TABLE VI Continued

Reference	*Intervention*	*Pts (n)*	*Neutropenia (%)*[a]	*Thrombocytopenia (%)*[a]	*Anemia (%)*[a]	*Peripheral neuropathy (%)*[a]	*Infection (%)*[a]	*Adverse events leading to discontinuation (%)*	*Treatment-related death (%)*	*Serious adverse events (%)*
Cavo *et al.*, 2010[15,h]	B–T–D→double ASCT	236	NR	NR	NR	10	3	6	<1	13
	T–D→double ASCT	238	NR	NR	NR	2	5	11	0	13
						p=0.0004	p=0.35	p=0.03		
Harousseau *et al.*, 2010[16]	V–Dox–D or V–Dox–D plus D–C–E–Cis	239	10	1.3	8.8	2.1	12.1[f]	13.4	2.9	33.9
	B–D or B–D plus D–C–E–Cis	239	5	2.9	4.2	7.1	8.8[f]	18.4	0	27.2
			p<0.05	p=NS	p<0.05	p<0.05	p=NS	p=NS	p=0.02	p=NS
Moreau *et al.*, 2011[28]	B–D	99	NR	0	3	11	14	0.4	NR	NR
	Reduced-dose B–T plus D	100	NR	3	3	3	10	0	NR	NR
						p=0.03				
Rosinol *et al.*, 2012[84] (abs.)	Maintenance:									
	B–T	90	NR	NR	NR	12.2	NR	15.6	NR	NR
	T	89	NR	NR	NR	10.1	NR	30.3	NR	NR
	Interferon	87	NR	NR	NR	0	NR		NR	NR
								p=0.08		
Sonneveld *et al.*, 2012[31]	Induction:									
	B–Dox–D→high-dose M plus ASCT	414	3	10	8	24	NR	27	2	46
				p<0.01		p<0.001				p<0.01
	Maintenance: B		0	4	1	5	NR	35	0	34
										p<0.01
	Induction:									
	V–Dox–D→high-dose M plus ASCT	413	1	5	7	10	NR	NA	2	36
	Maintenance: T		1	2	1	8	NR	NA	0	23
Relapsed or refractory disease										
Richardson *et al.*, 2005[23]	B 1.3 mg/m^2	331	14	30	10	8	NR	37	NS	NR
	D 40 mg	332	1	6	11	1	NR	29	NS	NR
			p<0.01	p<0.05		p<0.01[g]				

TABLE VI Continued

Reference	*Intervention*	*Pts (n)*	*Neutropenia (%)*[a]	*Thrombocytopenia (%)*[a]	*Anemia (%)*[a]	*Peripheral neuropathy (%)*[a]	*Infection (%)*[a]	*Adverse events leading to discontinuation (%)*	*Treatment-related death (%)*	*Serious adverse events (%)*
Orlowski *et al.*, 2007[20]	B 1.3 mg/m^2	318	15	16	9	9	NR	NR	4[d]	NR
	B 1.3 mg/m^2 plus peg-Dox 30 mg/m^2	318	29	23	9	4	NR	5	3[d]	NR
			$p<0.001$		p=NS	p=NS			p=NS	
Lonial *et al.*, 2010[17]	Escalating dose (B 1.0, 1.3, or 1.6 mg/m^2):									
	24 Hours before high-dose M	19	45	NR	NR	NR	16	NR	NR	NR
	24 Hours after high-dose M	20	65	NR	NR	NR	10	NR	NR	NR
							p=NS			
Reece *et al.*, 2011[22]	B 1.3 mg/m^2	21	NR	33	10	24	NR	33	NR	NR
	B 1.0 mg/m^2	21	NR	10	10	24	NR	24	NR	NR
Garderet *et al.*, 2012[30]	B–T–D	135	11	17	8	16	14	NR	NR	NR
	T–D	134	16	7	5	12	7	NR	NR	NR
						p=0.02				
Hjorth *et al.*, 2012[25]	B–D	64	17	34	NR	19	33	NR	NR	NR
	T–D	67	13	6	NR	7	24	NR	NR	NR
			p=NR	p=NR		p=NR				
Orlowski *et al.*, 2012[83] (abs.)	Siltuximab plus B	142	49	48	NR	NR	NR	NR	8	29
	B	144	NR	NR	NR	NR	NR	NR	5	24

[a] Grade 3 or 4 adverse events.
[b] Patients with pneumonia.
[c] In addition, bortezomib alone was discontinued in another 19% of patients.
[d] Deaths within 30 days after the last study medication.
[e] Adverse events reported during induction.
[f] A significant difference was reported for between-groups grades 1–4 herpes zoster ($p < 0.05$).
[g] Grade 3 adverse event.
[h] Adverse events reported during induction.

Pts = patients; ASCT = autologous stem-cell transplantation; B = bortezomib; M = melphalan; P = prednisone; NS = statistically nonsignificant; NR = not reported; abs. = abstract; T = thalidomide; D = dexamethasone; C = cyclophosphamide; L = lenalidomide; ATO = arsenic trioxide; V = vincristine; Dox = doxorubicin; E = etoposide; Cis = cisplatinum; peg-Dox = pegylated liposomal doxorubicin.

combination with thalidomide and dexamethasone was better than thalidomide and dexamethasone in improving OR and CR (45% vs. 25%, $p < 0.001$, and 45% vs. 11%, $p < 0.001$)[30].

QOL: The QLQ-C30 was used in two studies[25,36] to measure QOL. Lee *et al.*[36] reported QOL for patients in the VISTA trial (originally reported by Richardson *et al.*[23]). The authors assessed health-related QOL using the QLQ-C30[89] and adverse events with neurotoxicity symptoms using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity subscale[88,90]. Quality of life was assessed at baseline and every 6 weeks thereafter up to 42 weeks from baseline. A statistically significant difference in Global Health Status favouring bortezomib over dexamethasone during the 42 weeks of the study ($p = 0.001$) was reported. In addition, the authors reported a statistically significant difference in overall Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity score in favour of bortezomib ($p = 0.02$). On the other hand, Hjorth *et al.*[25] found no statistically significant difference between study arms comparing bortezomib with thalidomide (both combined with dexamethasone).

3.5 Toxicity

Question: What is the toxicity associated with the use of bortezomib?

3.5.1 Previously Untreated MM

Studies in the previously untreated population showed a significant increase in peripheral neuropathy in the bortezomib group when a drug combination including bortezomib was compared with a non-bortezomib-containing regimen[15,16,24,31]. In addition, San Miguel *et al.*[24] reported higher incidences of diarrhea and nausea in their bortezomib group than in their control group (8% vs. 1% and 4% vs. <1% respectively, p not reported). Table VI presents detailed data on adverse events.

The studies that compared various drug combinations containing bortezomib showed a higher incidence of neutropenia (38% vs. 28%, $p = 0.02$)[21] and peripheral neuropathy (10% vs. 2%, $p < 0.0004$)[15] with a 4-drug combination than with a 3-drug combination. A higher incidence of peripheral neuropathy was found when drug combinations with higher bortezomib doses were used (11% vs. 3%, $p < 0.003$)[28]. The incidence of neutropenia was also higher with a 3-drug combination containing an alkylating agent than with a 3-drug combination containing an immunomodulatory agent (39% vs. 22%, $p = 0.008$)[19]. Sonneveld *et al.*[31] reported a higher incidence of peripheral neuropathy in a bortezomib-containing combination (24% vs. 10%, $p < 0.01$). Palumbo *et al.*[21] also reported a higher incidence of cardiac events and thromboembolism with a 4-drug combination than with a 3-drug combination (10% vs. 5%, $p = 0.04$, and 5% vs. 2%, $p = 0.05$, respectively). Mateos *et al.*[19] showed that, compared with bortezomib combined with melphalan and an alkylating agent, a 3-drug combination including bortezomib and an immunomodulatory agent was favourable for a significantly lower incidence of thrombocytopenia, neutropenia, and infections (Table VI). However, the same study found a significant difference favouring the 3-drug combination including bortezomib and an alkylating agent for adverse events necessitating discontinuation of the drug and for overall serious adverse events (Table VI). The incidence of cardiac events was also significantly higher in the group that received bortezomib combined with an immunomodulatory agent than in the group that received a combination of bortezomib and an alkylating agent (8% vs. 0%, $p = 0.001$)[19]. Kumar *et al.*[26] reported a higher incidence of treatment-related deaths from renal failure in the 4-drug combination that included an immunomodulatory and an alkylating agent (Table VI).

3.5.2 Relapsed and Refractory MM

Our review found a higher incidence of hematologic events (Table VI) and peripheral neuropathy, and a significantly higher incidence of diarrhea and nausea (7% vs. 2% and 2% vs. 0% respectively, $p < 0.01$), in patients with relapsed or refractory MM who received bortezomib than in those who received dexamethasone (control)[23]. Orlowski *et al.*[20] also showed an increased incidence of neutropenia (Table VI), diarrhea, and nausea in a bortezomib–PLD group than in a bortezomib-alone group (7% vs. 4%, $p = 0.034$, and 2% vs. <1%, $p = 0.0241$, respectively). A higher incidence of peripheral neuropathy and thrombocytopenia was observed by Sonneveld *et al.*[31] in patients who received bortezomib in combination with other drugs than in those who received bortezomib alone or a non-bortezomib-containing drug combination (24% vs. 10%, $p < 0.001$, and 10% vs. 5%, $p < 0.01$). When various doses of bortezomib were compared, Moreau *et al.*[28] also showed a higher incidence of peripheral neuropathy with higher doses of bortezomib (11% with full dose vs. 3% with reduced dose, $p = 0.03$).

Adverse events leading to discontinuation of treatment occurred in 37% of a bortezomib group compared with 29% of a dexamethasone group (reported by Richardson *et al.*[23]). A corollary report from the APEX study[23] by Chanan–Khan[35] examined the incidence of herpes zoster events in patients treated with bortezomib. The authors found that a significantly higher incidence of herpes zoster was associated with bortezomib than with the control dexamethasone treatment (13% vs. 5%, $p = 0.0002$).

3.6 Subgroups

Question: Which patients are more or less likely to benefit from treatment with bortezomib?

3.6.1 Previously Untreated MM

The combination of melphalan–prednisone–bortezomib produced better results than did melphalan–prednisone[24] in these subgroups:

- Patients 75 years of age and older: TTP was identical in the younger and older groups; CR was 26% in the older group and 32% in the younger group, $p = 0.29$; OS, $p = 0.17$
- Patients with impaired renal function: CR, TTP, and OS did not differ for 159 patients with normal renal function and for 185 patients with a creatinine clearance less than 60 mL/min

Also, although cytogenetic studies were not available in all participants, the 26 patients with a high-risk cytogenetic profile [t(4;14), t(14;16), and del17p] did not differ from the 142 patients with a standard profile in CR (both groups: 28%), TTP ($p = 0.55$), and OS ($p = 0.99$)[24].

In the study by Mateos *et al.*[19], patients with cytogenetic abnormalities [t(4;14), t(14;16), and del17p (44 vs. 187)] in both treatment groups did not differ for CR, but experienced shorter PFS and OS at induction (HR: 0.6, $p = 0.01$, and HR: 0.5, $p = 0.01$, respectively) and maintenance ($p = 0.01$ and $p < 0.0001$ respectively). In the study by Neben *et al.*[71], a companion study of the HOVON-65 study[31], patients with all chromosomal aberrations treated with bortezomib–doxorubicin–dexamethasone experienced a PFS and OS similar or superior to those of patients treated with vincristine–doxorubicin–dexamethasone. The patients that seemed to benefit more from bortezomib treatment had del(17p13): their PFS duration was 26.2 months compared with 12 months in peers not receiving bortezomib ($p = 0.024$); the associated 3-year OS rates were 69% and 17% ($p = 0.028$).

3.6.2 Relapsed or Refractory MM

Extensive subset analyses have been performed using data from the APEX trial[23] of bortezomib compared with dexamethasone for relapsed or refractory myeloma[32–39]. Bortezomib was consistently superior to dexamethasone in patients 65 years of age and older (response rate: $p = 0.0004$; TTP: $p = 0.002$); in patients with International Staging System stage II and III disease (response rate: $p < 0.0004$; TTP: $p = 0.0002$); in patients refractory to the most recent therapy and in those who had previously received more than one line of therapy (both subgroups—response rate: $p < 0.0001$; and TTP: $p < 0.0001$)[32]; and in patients with renal impairment[34]. Similarly, bortezomib–PLD was more efficacious than bortezomib alone in most subgroups analyzed, including patients of any age; patients with refractory disease; patients with elevated β_2-microglobulin; and patients previously exposed to ASCT, anthracyclines, and immunomodulatory drugs (thalidomide or lenalidomide)[20,41]. An advantage for bortezomib–PLD compared with bortezomib alone was also observed in patients with cytogenetic abnormalities except for deletion 13q[20].

4. DISCUSSION

Introduction of the melphalan–prednisone–bortezomib combination in newly diagnosed MM patients significantly improved outcome in patients who are not candidates for ASCT[24]. Eligible patients include those more than 65–70 years of age and those with concomitant medical conditions felt to increase the risks of ASCT. Compared with melphalan and prednisone alone, melphalan–prednisone–bortezomib in a finite course (9 cycles) improved TTP and OS and resulted in better OR and CR rates. Surprisingly, hematologic toxicity was not increased, and other toxicity rates were similar to those observed in various series using bortezomib. Melphalan–prednisone–bortezomib was superior in all patient subgroups and might have particular benefit in patients with poor prognostic factors in whom melphalan–prednisone has limited efficacy, such as patients with a high β_2-microglobulin level and adverse cytogenetics.

Making a direct comparison to initial therapy with melphalan–prednisone–thalidomide is difficult. A previously reported systematic review[91] that forms the evidence base of an earlier practice guideline (evidence-based series report #6–21: *Thalidomide in Multiple Myeloma*)[92] indicated that melphalan–prednisone–thalidomide is the preferred treatment option for patients with MM who are not eligible for ASCT. However, given the lack of actual comparative evidence and the recognition that thalidomide can be difficult to obtain or to tolerate, physicians and patients might choose to initiate therapy with bortezomib-containing therapy—a choice that is currently supported by a network meta-analysis that showed no difference for all outcomes and a significant benefit for CR (RR: 2.34; 95% CI: 1.12 to 4.90) and for grades 3 and 4 adverse events (RR: 0.53; 95% CI: 0.38 to 0.73) in favour of bortezomib[10]. In particular, bortezomib-based therapy might be preferred in patients with disease-related renal dysfunction or cytogenetic abnormalities. Studies testing lenalidomide and dexamethasone as an upfront option are still ongoing, with no results yet available (search for NCT01554852 at http://clinicaltrials.gov/).

In MM, most studies have indicated that patients who achieve a CR, a near-CR (same as CR, but residual monoclonal protein by immunofixation only), or in some instances, a very good partial remission (defined as >90%), particularly after ASCT, have superior rates of PFS and OS compared with lesser degrees of response. Many phase II studies of combination regimens containing novel agents such as bortezomib as first-line therapy have reported higher rates of CR, near-CR, or very good partial remission before ASCT compared with the rates observed with older regimens such as vincristine–doxorubicin–dexamethasone or

dexamethasone alone. One approach to improving the results of ASCT therefore involves using novel agents upfront so that patients will go into transplantation with a greater depth of remission (on the hypothesis that rates of CR or near-CR, and hence survival, will be improved after ASCT). Several phase III randomized trials comparing bortezomib-containing induction regimens were designed to test that hypothesis[15,16]. Those trials found a statistically significant better CR and a favourable PFS in the bortezomib arm. In addition, two studies further supported the use of bortezomib before ASCT. In the study by Sonneveld *et al.*[31], an OS benefit was suggested for a bortezomib-based combination before ASCT given with bortezomib-based consolidation after ASCT. The DSG is also aware of a study-level meta-analysis, so far published only in abstract form and therefore excluded from this systematic review, which supports a survival benefit with the use of bortezomib before ASCT[93]. Given the benefits and the recognized toxicities associated with earlier chemotherapy-based regimens, the DSG considers bortezomib-based induction to be a recommended option before ASCT.

Despite effective first-line therapy, nearly all MM patients eventually relapse and require further therapy. Options for the management of recurrent MM include reinstitution of the initial treatment if the duration of response was prolonged, a second ASCT as salvage therapy, alkylating agents with corticosteroids, high-dose dexamethasone, or thalidomide alone or in combination with corticosteroids. Lenalidomide is now approved by Health Canada for use with dexamethasone in the treatment of MM that has progressed after at least 1 prior treatment regimen. Many phase I–II trials have combined novel agents, particularly bortezomib, with conventional cytotoxic agents or other novel agents as first-line therapy. Evidence fr om RCTs supports the use of bortezomib in combination with PLD in patients with relapsed or refractory MM[20]. In patients who cannot tolerate that therapy, the use of bortezomib alone for relapsed or refractory disease is recommended by the DSG.

The Hematology DSG has already recommended bortezomib monotherapy for patients with MM refractory to or relapsing within 1 year of the conclusion of initial or subsequent treatments and who are candidates for further therapy[94]. That recommendation was made based on the benefit in OS and TTP observed in the APEX trial[23]. The extended follow-up of APEX reported by Richardson *et al.*[33] indicates that the benefit still exists. In relapsed and refractory MM, bortezomib monotherapy and combination therapy with PLD are both effective approaches. However, compared with bortezomib alone, the combination with PLD improves TTP, PFS, and OS significantly[20]. The magnitude of the benefit for the combination of bortezomib and PLD is identical to that seen for bortezomib alone compared with dexamethasone in the original pivotal trial of bortezomib, the APEX trial[23,33]. However, whether the benefit applies to all patients with MM is unknown, because the authors excluded patients who had previously received more than 240 mg/m^2 or an equivalent dose of doxorubicin[20]. Particular advantages of the PLD–bortezomib combination are its avoidance of the use of corticosteroids (which are required in most of the other anti-MM regimens), its efficacy in high-risk groups, and its effectiveness after prior exposure to immunomodulatory derivatives. However, the combination is associated with more toxicity—specifically, myelosuppression, gastrointestinal toxicity, and hand–foot syndrome. Bortezomib monotherapy might therefore be preferable in patients with coexisting medical conditions or in frail patients.

5. CONCLUSIONS

In patients with previously untreated MM who are not candidates for ASCT, bortezomib combined with melphalan and prednisone is the preferred first-line therapy. In patients who are eligible for ASCT, bortezomib-based induction before transplantation is a recommended option.

In patients with relapsed or refractory MM, the combination of PLD plus bortezomib is a more effective treatment option than is bortezomib alone. The combination can be considered for use in patients with a cumulative doxorubicin dose less than 240 mg/m^2 (or the equivalent). In patients with poor steroid tolerance, with brittle bones, or with diabetes mellitus, this combination is particularly useful. For individuals who cannot access or tolerate this therapy, treatment with bortezomib alone is recommended. Consideration should be given to the use of antiviral prophylaxis against herpes zoster (shingles), because that condition is now recognized to occur more frequently during bortezomib therapy[23,35].

For specific details related to the administration of bortezomib therapy, the authors suggest that clinicians refer to the protocols used in the major trials and to the product monograph. Most toxicities are reversible if dose modification guidelines are followed.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors of this report disclosed potential conflicts. One author (DER) was the principal investigator or the local investigator and received research funding for four trials. DER was also a consultant for

the manufacturer of bortezomib, an advisory board participant for a future trial, and received honoraria. One other author (TCK) received honoraria while acting as a consultant for the manufacturer of bortezomib and was an advisory board participant. All other authors declared no financial conflicts of interest.

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