

Haematology News

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A review of bortezomib data in high-risk multiple myeloma

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Abstract

Multiple myeloma is characterised by a number of factors that are typically associated with a poor outcome to conventional treatments, such as advanced age, the presence of renal impairment and cytogenetic abnormalities. The availability of novel agents has led to substantial changes in treatment practices and may offer a particular benefit to patients with high-risk disease. Bortezomib is a first in class proteasome inhibitor that is approved in the frontline setting in combination with melphalan and prednisone for the treatment of patients not eligible for stem cell transplantation and as monotherapy for progressive disease for patients who have received at least one prior treatment. The pivotal Phase 3 trials that led to the approval of bortezomib included patients with various risk factors, and the data indicate that bortezomib efficacy is maintained in these patients. This review provides a summary of bortezomib data in the setting of advanced age, renal impairment, cytogenetic abnormalities and bone disease in the approved settings.

Introduction

Multiple myeloma (MM) is a malignant neoplasm characterised by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow. It is manifested by skeletal destruction, renal impairment, anaemia and hypercalcaemia. A number of patient and disease factors have been identified that are typically associated with a poor prognosis. These include elevated β_2 -microglobulin (β_2 M) and low serum albumin levels, advanced age and the presence of particular cytogenetic abnormalities or comorbidities, for example renal impairment (Stewart *et al*, 2007; Ludwig *et al*, 2008).

Although MM remains incurable with current treatment approaches, the outcome for patients diagnosed with the malignancy has improved markedly over recent years due to advances in therapy, as well as supportive care (Kristinsson *et al*, 2007; Kumar *et al*, 2008). The novel agents thalidomide, bortezomib and lenalidomide are increasingly being incorporated into treatment strategies and have substantially improved response rates and in some cases survival compared with conventional therapy (Facon *et al*, 2007; Richardson *et al*, 2007a; San Miguel *et al*, 2008a; Dimopoulos *et al*, 2009a; Hulin *et al*, 2009). It is of interest to investigate the novel agents in the setting of high-risk disease which presents a particular challenge due

to reduced efficacy of conventional therapy in this setting.

This article provides an overview of bortezomib data in patients with high-risk disease characterised by the presence of advanced age, renal impairment, cytogenetic abnormalities and bone disease, and will focus on the available data in the approved indications.

Bortezomib is a potent and reversible inhibitor of the proteasome that is approved in combination with melphalan and prednisone for the treatment of patients with newly diagnosed MM who are not eligible for transplantation based on the results of the Phase 3 VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone) trial. In this study the combination of bortezomib, melphalan and prednisone (VMP) was compared to melphalan and prednisone (MP) in patients with newly diagnosed MM who were not eligible for transplantation. A significant superiority was demonstrated for the VMP regimen for all pre-specified parameters, including overall response rate (ORR), complete response (CR), duration of response (DOR), time to progression (TTP) and overall survival (OS) (San Miguel *et al*, 2008a).

The results of the Phase 2 SUMMIT (Study of Uncontrolled Multiple

Myeloma Managed with Proteasome Inhibition Therapy) and the Phase 3 APEX (Assessment of Proteasome Inhibition for Extending Remissions) trials formed the basis for the approval of bortezomib in the relapsed/refractory setting. In the SUMMIT trial, a response rate (CR+PR) of 27% was achieved with single-agent bortezomib in heavily pretreated patients with relapsed and refractory MM with 10% durable CR or near CR (nCR) obtained (Richardson *et al*, 2003). The pivotal Phase 3 APEX study demonstrated the superiority of bortezomib over dexamethasone in patients with MM whose disease relapsed after one to three prior therapies. With bortezomib monotherapy, an ORR of 43% and a CR+nCR rate of 16% were observed compared with 18% and 2% respectively for dexamethasone; TTP was 6.2 months and OS was 29.8 months with bortezomib versus 3.5 months and 23.7 months respectively with dexamethasone (Richardson *et al*, 2005, 2007a). The difference in survival was significant, despite more than 62% of patients on the dexamethasone arm crossing over to receive bortezomib.

These pivotal trials have established bortezomib as a key component of MM therapy and the results in different patient populations obtained from the APEX and VISTA trials are summarised below.

Bortezomib for the treatment of elderly patients

Whereas the long-term survival for young patients has improved over recent years (Brenner *et al*, 2007), age has remained a significant risk factor when treatment with conventional MM therapy is administered (Ludwig *et al*, 2008). However, with the incorporation of novel agents, such as thalidomide, bortezomib and lenalidomide, into the treatment strategies for elderly patients, the outlook for this patient group is improving.

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Bortezomib was investigated in combination with MP in the Phase 3 VISTA trial in comparison with the traditional MP regimen in patients with previously untreated MM ineligible for stem cell transplantation (San Miguel *et al*, 2008a). The trial enrolled 682 patients from 151 centres in 22 countries worldwide. The median age of patients was 71 years; notably nearly a third of patients were ≥ 75 years old. In addition, a third of patients had a Karnofsky performance status of ≤ 70 , a third of patients had $\beta_2M > 5.5$ mg/L and 58% of patients had low albumin (albumin < 3.5 g/dL). Patients in the MP arm received nine six-week cycles of melphalan at 9 mg/m² and prednisone at 60 mg/m² once daily on days 1–4. Treatment in the VMP arm consisted of the same melphalan and prednisone regimen plus bortezomib at 1.3 mg/m² twice weekly on weeks 1, 2, 4 and 5 for four six-week cycles (eight doses per cycle), followed by bortezomib administered once weekly during weeks 1, 2, 4 and 5 for five six-week cycles (four doses per cycle).

The ORR, determined using EBMT criteria, was 71% with VMP compared with 35% with MP, with an immunofixation-negative CR rate of 30% with VMP versus 4% with MP ($P < 0.001$) (San Miguel *et al*, 2008a). TTP was significantly longer in the VMP arm than in the MP arm (24 months versus 16.6 months, $P < 0.001$). At a median follow-up of 36.7 months, median survival was not reached in the VMP arm and was 43.1 months in the MP arm ($P = 0.0008$) (Mateos *et al*, 2009a). VMP demonstrated a superior 3-year OS rate compared with MP: 68.5% versus 54%. In addition, median time to next therapy (TNT) and median treatment-free interval (TFI) were longer with VMP than MP: median TNT was 28.1 versus 19.2 months ($P < 0.001$); median TFI was 17.6 versus 8.4 months ($P < 0.001$), respectively.

The benefit of achieving a high CR rate was demonstrated in a subanalysis that investigated the outcome in patients attaining CR or not. Patients who achieved CR were found to have longer TTP, TFI and TNT compared with patients who achieved PR (Harousseau *et al*, 2009). Achievement of CR was also associated with improvement in quality of life (Dhawan *et al*, 2009).

Furthermore, in patients who received subsequent therapy, OS from randomisation was longer with VMP versus MP ($P = 0.021$) (3-year OS rates were 67.9% versus 55.9%, respectively) (Mateos *et al*, 2009a). VMP resulted in longer OS, despite 50% of MP patients receiving bortezomib in a subsequent line of therapy.

In addition to demonstrating efficacy, tolerability is a key factor when assessing treatments for the elderly population. Overall, VMP was found to be well tolerated and the addition of bortezomib did not increase toxicity for the majority of adverse events (AEs). The main differences in the incidence of grade 3/4 adverse events between the VMP and MP arms were seen for gastrointestinal side effects, peripheral neuropathy (PN) and Herpes zoster, which were found to be more frequent in the VMP arm; grade 3 GI adverse events were observed in 19% of patients receiving VMP versus 5% of patients receiving MP; Herpes zoster was more frequent with VMP (13% versus 4%); however, among patients receiving antiviral prophylaxis, the incidence with VMP was only 3% (San Miguel *et al*, 2008a). PN grade 3 was observed in 13% of patients, but grade 4 was observed in $< 1\%$ of patients receiving VMP. However, PN was reversible in most patients; 79% of PN events improved (≥ 1 grade) in a median of 1.9 months and 60% of PN events completely resolved in a median of 5.7 months (Mateos *et al*, 2009b). Haematological toxicities were similar between the VMP and MP arms: thrombocytopenia (grade ≥ 3 38% versus 31%), neutropenia (grade ≥ 3 40% versus 38%) anaemia (grade ≥ 3 19% versus 27%) and lymphopenia (grade ≥ 3 20% versus 11%) for VMP versus MP, respectively (Richardson *et al*, 2009a). The rate of platelet transfusions was slightly higher in the VMP compared to the MP arm (12% versus 9%), whereas the use of granulocyte-stimulating factor (G-CSF) was similar (25% versus 26%) and the use of erythropoiesis-stimulating agents (ESAs) and red blood cell transfusions (RBCT) was lower in the VMP arm versus the MP arm (ESAs, 30% versus 39%; RBCT, 26% versus 35%) (Richardson *et al*, 2009b). In addition, ESA use was not found to adversely impact long-term outcomes with VMP or MP and was not associated with an increased risk of thrombo-embolic complications. Rates of DVT and PE were low with VMP and MP (1% versus 2% and 1% versus 1%, for VMP and MP respectively).

A subanalysis of the VISTA trial showed that VMP was more effective than

In addition to demonstrating efficacy, tolerability is a key factor when assessing treatments for the elderly population



MP in patients <75, as well as in those ≥75 years of age (Table 1) (Figure 1) (Kropff *et al*, 2009). Tolerability was similar across the two age groups, apart from a higher incidence of serious AEs (SAEs) in the group of patients ≥ 75 years, which occurred in both the MP and VMP arms, indicating that this may not be due to the addition of bortezomib to MP. An analysis of OS for patients receiving VMP revealed that after a median follow-up of 36.7 months there was a significant difference in OS in patients <75 years compared to those ≥75 years old (median OS not reached for patients <75 years versus 43.3 months for patients ≥75 years, $P = 0.011$; 3-year OS rate, 74.1% versus 55.5% respectively) (Mateos *et al*, 2009a). The investigators concluded that this difference in OS likely reflects the known adverse impact of advanced age on survival.

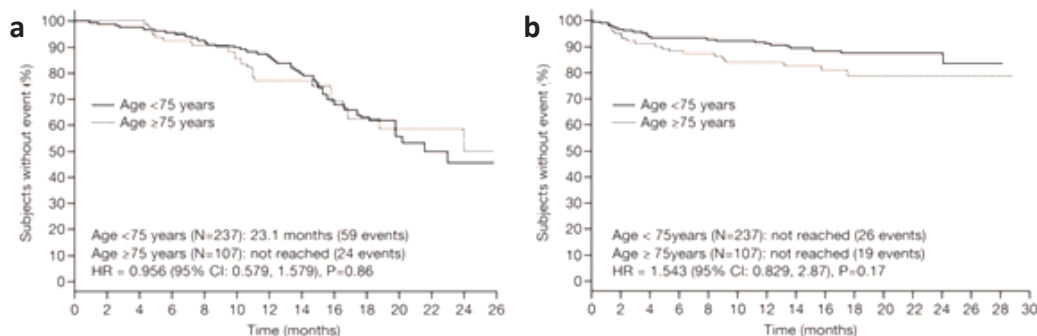
These results are significant as they establish VMP as a treatment option for newly diagnosed patients not eligible for transplantation and show that the combination is a feasible option even for very elderly patients.

In the relapse setting, bortezomib has also been shown to be effective in elderly patients. A subanalysis of the APEX trial showed that patients ≥65 years old treated with bortezomib did not appear to have lower response rate, TTP or 1-year survival probability than patients aged <65 years (Table 2) (Richardson *et al*, 2007b). In addition, the safety profile for bortezomib was comparable between the two patient groups.

A further subanalysis investigated the efficacy of bortezomib versus dexamethasone in patients ≥75 years. Although only a small number of patients were of advanced age ($n = 27$ ≥75 years in each of the treatment arms), the data suggest that bortezomib is superior to dexamethasone in these elderly patients with relapsed MM with regard to ORR (50% versus 19%), median TTP (9.1 versus 4.1 months) and median OS (30 versus 10 months) (Kropff *et al*, 2009).

In summary, bortezomib data in the frontline and relapse settings indicate that the agent is an effective option for elderly patients with manageable side effects.

Figure 1: VISTA: TTP (a) and OS (b) for patients receiving VMP according to age subgroup (< 75 years versus ≥ 75 years) (San Miguel *et al*, 2008a)



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Table 1: VISTA subanalysis: response, TTP, OS by age subgroup (Kropff *et al*, 2009)

		CR + PR (%)	CR (%)	Median TTP (months)	2/3-year OS (%)
Age ≥75 years	VMP ($n = 106$)	60*	26*	Not reached*	74/60
	MP ($n = 100$)	40	3	16.4	58/44
Age <75 years	VMP ($n = 231$)	75*	32*	23.1*	79/77*
	MP ($n = 231$)	32	4	17.4	73/65

*Statistically significant difference between VMP and MP arms.

Table 2: APEX subanalysis: response, TTP, OS by age subgroup (Richardson *et al*, 2007b)

		CR + PR (%)	Median TTP (months)	1-year OS (%)
Age ≥65 years	Bortezomib ($n = 125$)	40*	5.5*	79*
	Dexamethasone ($n = 120$)	18	4.3	63
Age <65 years	Bortezomib ($n = 208$)	38*	6.3*	81*
	Dexamethasone ($n = 216$)	18	2.9	69

*Statistically significant difference between bortezomib and dexamethasone arms.



Bortezomib in patients with renal impairment

Renal impairment is a serious complication of MM, which affects a significant subgroup of patients. At presentation, up to 50% of patients with MM have some degree of renal dysfunction, and 20%–30% of patients may have renal failure (Bladé *et al*, 1998). Renal impairment is associated with an increased occurrence of complications and a poorer outcome overall compared to patients with normal renal function. It requires prompt action with the aim of preventing further deterioration of renal function by reducing tumour burden and removing excess light chains. In parallel, supportive care measures, such as hydration, should be initiated to salvage and improve renal function.

Bortezomib is an attractive agent for investigation in patients with renal impairment because of its rapid onset of action that typically results in a response within the first two treatment cycles (Richardson *et al*, 2007a). In addition, the pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (creatinine clearance [CrCl] > 20 mL/min/1.73 m²), so dose adjustments for these patients are not necessary (Bortezomib EU prescribing information). It is not known if the pharmacokinetics of bortezomib are affected by the presence of severe renal impairment (CrCl < 20 mL/min/1.73 m²) in patients not undergoing dialysis. In patients undergoing dialysis treatment, bortezomib should be administered after dialysis, as the procedure may reduce bortezomib concentrations (Bortezomib EU prescribing information).

An exploratory subgroup analysis of the APEX study was conducted to assess the efficacy and safety profiles of bortezomib in patients with different degrees of renal impairment who were included in the trial (San Miguel *et al*, 2008b). Patients in each arm were divided into the following subgroups defined by their degree of renal impairment at baseline in terms of calculated creatinine clearance: CrCl of <30, 30–50, 51–80 and >80 mL/min, which corresponded to severe, moderate, mild and no renal impairment, respectively (patients in the APEX trial were required to have a calculated CrCl of ≥20 mL/min). Bortezomib was more effective than dexamethasone across all renal subgroups (Table 3) (San Miguel *et al*, 2008b). In addition, within the group of patients treated with bortezomib, ORR, median time to first response, as well as TTP and OS were similar in patients with severe to moderate renal impairment and those with no or mild renal impairment. In addition, the toxicity profile for bortezomib was found to be similar in patients with and without renal impairment and the number of patients discontinuing treatment or requiring dose reduction was also found to be comparable.

In a subanalysis of the Phase 3 VISTA trial, patients were divided into groups depending on their degree of renal impairment as defined by baseline glomerular filtration rate (GFR) (Dimopoulos *et al*, 2009b). Normal renal function was defined as GFR > 50 mL/min and renal impairment (≤50 mL/min) was subdivided into moderate (31–50 mL/min) or severe (≤30

Table 3: APEX subanalysis: response rate, TTP and OS by renal subgroup (San Miguel *et al*, 2008b)

	Bortezomib				Dexamethasone			
	Creatinine clearance (mL/min)				Creatinine clearance (mL/min)			
	<30	30–50	51–80	>80	<30	30–50	51–80	>80
Response-evaluable pts	15	43	137	118	10	52	118	123
CR + PR (%)	47	37	40	36	10	17	25	11
CR (%)	0	9	8	4	0	2	0	1
Median time to first response (months)	1.6	0.7	1.2	1.4	1.4	0.8	1.4	1.4
Median TTP (months)	4.2	5.6	6.2	6.3	2.1	2.9	4.9	2.8
Median OS (months)	22	22.8	30	NE	17.4	12.6	24.3	29.1

NE, not estimable.



mL/min). About a third of patients on each arm presented with predominantly moderately impaired renal function. Patients with serum creatinine levels higher than 2 mg/dL were excluded from the trial because of the melphalan component of the chemotherapy being used in the study.

VMP was found to be active and well tolerated in elderly, previously untreated patients with moderate or severe renal impairment (Dimopoulos *et al*, 2009b). ORR, CR, time to response, duration of response, TTP and OS were superior with VMP compared with MP (Table 4). For both arms, TTP appeared similar in patients with and without renal impairment whereas OS appeared to be longer in patients with normal renal function (Figure 2). In addition, reversal of renal impairment, defined as an improvement in GFR from <50 mL/min at baseline to >60 mL/min on treatment, was assessed. VMP resulted in the reversal of renal impairment in 44% of patients, whereas with MP reversal of renal impairment was observed in 34% of patients. Time to reversal of renal impairment in patients with baseline GFR < 50 mL/min was significantly shorter with VMP versus MP (9 versus 13.6 months, $P = 0.03$). An analysis of factors influencing the rate of renal impairment reversal found that age <75 years and less severe renal impairment (GFR ≥ 30 mL/min) were associated with a higher rate of reversal (multivariate analysis).

Although rates of grade 4 and 5 AEs and SAEs on the VMP arm were higher in patients with renal impairment versus those without renal impairment, overall treatment duration and rates of discontinuation and dose reduction of bortezomib were comparable between patients with and without renal impairment. Notably, the rate of \geq grade 3 PN was comparable across patient subgroups in the VMP arm.

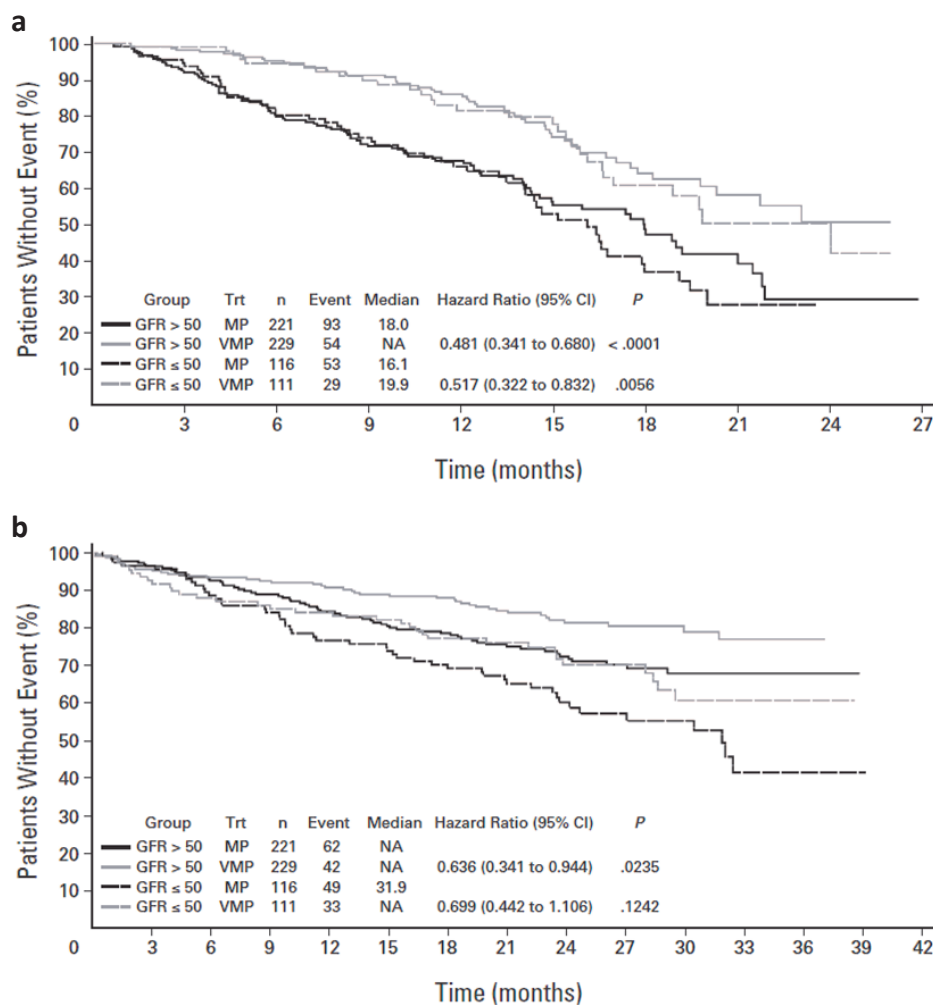
Taken together, the results of these subanalyses suggest that bortezomib and VMP are effective in patients with renal impairment and that AEs are comparable to those observed in patients with normal renal function.

Table 4: VISTA subanalysis: response rate, TTP and OS by renal subgroup (Dimopoulos *et al*, 2009b)

	VMP			MP		
	GFR (mL/min)			GFR (mL/min)		
	≤ 30	31–50	>50	≤ 30	31–50	>50
Response-evaluable pts	19	92	226	15	99	217
CR + PR (%)	74	67	72	47	45	29
CR (%)	37	29	30	13	4	3
Median time to first response (months)	1.0	1.1	1.4	3.5	3.3	4.9
Median duration of response (months)	18.5	16.3	22.4	10.8	13.1	20.5
Median TTP (months)	19.8	24	NE	14.5	16.1	18
Median OS (months)	28.7	NE	NE	24.7	NE	NE

NE, not estimable. GFR, glomerular filtration rate.

Figure 2: VISTA subanalysis: (a) TTP and (b) OS in VMP and MP arms in patients with normal and impaired renal function (Dimopoulos *et al*, 2009b)



Normal renal function: GFR > 50 mL/min
Impaired renal function: GFR \leq 50 mL/min

Dimopoulos, M *et al*: *J Clin Oncol* 27(36), 2009:6086-93. Reprinted with permission.
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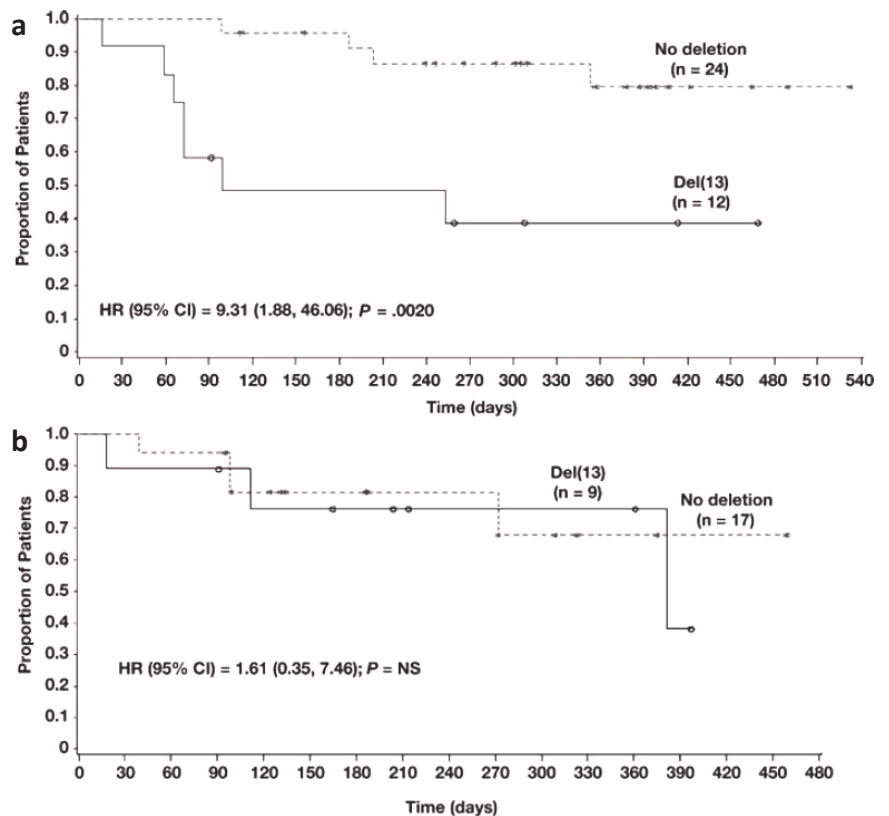
Bortezomib in patients with cytogenetic abnormalities

Over the recent past an increased understanding of myeloma disease biology has led to the identification of a number of cytogenetic factors that are associated with a poor prognosis. The presence of hypodiploidy, deletion of chromosome 13 (del13) as detected by metaphase cytogenetics, as well as deletion of chromosome 17 (del17) and translocations of chromosomes 4 and 14 (t(4;14)) and 14 and 16 (t(14;16)) detected by fluorescence *in situ* hybridisation (FISH) are characteristic of high-risk disease (Stewart *et al*, 2007).

Novel agents are being investigated in the setting of high-risk disease to assess if their application may improve outcomes. In a matched-pair analysis of the APEX relapse study, the effect of del13, detected by metaphase

cytogenetics, on response, TTP and OS with bortezomib and dexamethasone were investigated. Response rates were not significantly different in patients with and without del13 in either arm. In nine patients who had del13 by metaphase cytogenetics and who received bortezomib, the ORR was 25%, whereas in 17 patients without the deletion bortezomib treatment resulted in an ORR of 35% ($P = ns$). For the dexamethasone arm, the ORR for 12 patients with del13 by metaphase cytogenetics was 9% and it was 26% for 24 patients without del13 ($P = ns$) (Jagannath *et al*, 2007). However, OS was significantly shorter for dexamethasone-treated patients with del13 compared to those without the deletion, whereas in the bortezomib arm OS was comparable in both groups (Figure 3).

Figure 3: APEX subanalysis: OS according to del13 status by metaphase cytogenetics in (a) dexamethasone-treated patients and (b) bortezomib-treated patients (Jagannath *et al*, 2007)



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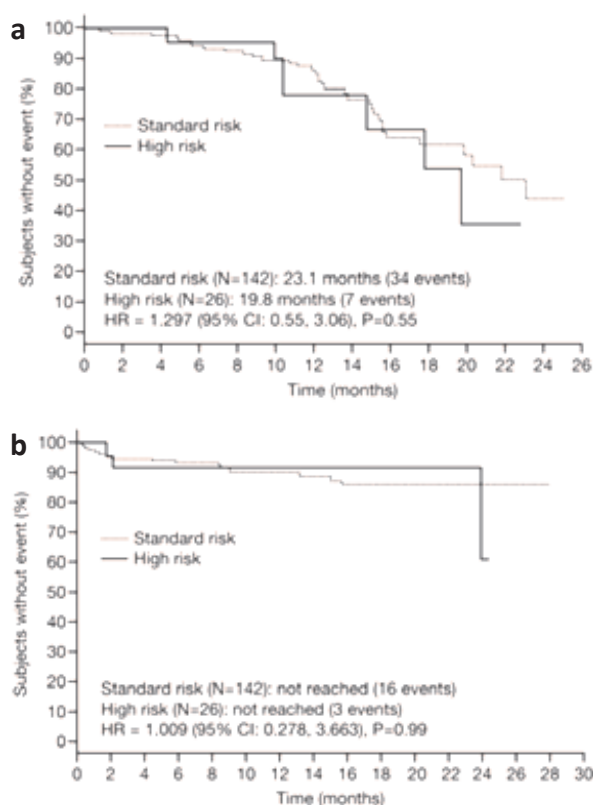


In patients with newly diagnosed disease not eligible for transplantation, the presence of high-risk cytogenetic abnormalities does not appear to affect response, TTP and OS with VMP, as observed in an analysis of 26 patients with t(4;14), t(14;16) or del17 detected by FISH. CR in this group of patients was 28% compared with 30% in the overall VMP group. TTP was 19.8 months in the high-risk group versus 23.1 months in patients with standard-risk disease ($n = 142$) ($P = 0.55$), and OS at a median follow-up of 16.3 months was similar in both arms (Figure 4). In addition, with a median follow-up of 36.7 months, OS was not significantly different between the two groups ($P = 0.399$); however, there was a trend to longer OS in patients with standard-risk cytogenetics (3-year OS: 71.6% for patients with standard-risk disease versus 56.1% for patients with high-risk disease) (Mateos *et al*, 2009a).

In patients with newly diagnosed disease not eligible for transplantation, the presence of high-risk cytogenetic abnormalities does not appear to affect response to bortezomib-based therapy

Collectively, these data suggest that bortezomib or bortezomib combinations remain effective despite the presence of cytogenetic abnormalities, such as del13 detected by metaphase cytogenetics, or del17 and translocations t(4;14) and t(14;16) detected by FISH analysis. However, it should be noted that patient numbers were limited and that these results require confirmation in large, randomised studies.

Figure 4: VISTA: TTP (a) and OS (b) for patients receiving VMP according to presence or absence of adverse cytogenetic features (San Miguel *et al*, 2008a)



Bortezomib in myeloma bone disease

Bone disease is one of the most debilitating manifestations of MM and it has a severe impact on patients' quality of life. Most patients have bone lesions at diagnosis, and almost all will develop skeletal complications, including bone pain, osteolytic lesions, pathological fractures and hypercalcaemia during the course of their disease (Kyle, 1975; Roodman, 2008). Bortezomib is being investigated in the setting of bone disease based on observations of a possible positive effect of the agent on bone remodelling.

In the APEX trial, a significant elevation in serum alkaline phosphatase (ALP), a marker of bone formation, in bortezomib-responsive patients was observed, which was significantly higher than in those patients responding to dexamethasone (Zangari *et al*, 2005). These results indicate that the anti-myeloma activity of bortezomib may be associated with an activation of osteoblasts.

A further analysis of data from the Phase 3 APEX trial assessed the relationship between quantitative total ALP changes and response and time to progression during therapy with bortezomib. The analysis found that a 25% increase in total ALP at 6 weeks was strongly associated with patients achieving a response and longer time to myeloma progression (Zangari *et al*, 2007). The investigators concluded that markers of osteoblast activation may be useful in predicting response to bortezomib and duration of response.

A subanalysis of the VISTA trial, which focused on bone disease by analysing changes in ALP from baseline in the two treatment arms, found that patients on the VMP arm appeared to experience fewer skeletal events and required less bisphosphonate use than patients receiving MP (Delforge *et al*, 2009). In addition, patients on the VMP arm demonstrated greater increases in ALP than patients on the MP arm, suggesting that there is greater osteoblastic stimulation with VMP compared with MP. Increases in ALP were also strongly associated with response to VMP, an observation that was also made with single-agent bortezomib in the APEX trial.

These results suggest that bortezomib may combine potent anti-myeloma activity with beneficial effects on bone. However, to date, evidence of the effect of bortezomib on clinical endpoints specific to bone is limited and prospective trials investigating endpoints related to bone formation are needed.

Conclusion

The availability of a number of effective novel agents has led to improvements in overall outcome for patients. Notably, results indicate that some of the novel agents remain effective in the presence of factors that have traditionally been associated with a poor prognosis to treatment with conventional agents. Bortezomib has been investigated in a number of high-risk groups and results from subanalyses of the APEX and VISTA trials indicate that the agent is effective in elderly patients with MM in the frontline, as well as the relapse setting, and has an acceptable toxicity profile. In addition, these trials indicate that bortezomib is a feasible treatment in patients with moderate renal impairment and can lead to improvement in renal function in up to 44% of patients. In patients with high-risk cytogenetic abnormalities, the data suggest that bortezomib retains efficacy; however, because of the limited number of patients with adverse cytogenetic factors in these trials, confirmation of the results from larger studies is needed. Finally, a positive effect on bone disease of bortezomib has been reported, although a demonstration of improve-



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ments regarding relevant clinical endpoints is required. Taken together, these results support the use of bortezomib irrespective of the presence of high-risk disease features.

Bortezomib may combine potent anti-myeloma activity with beneficial effects on bone



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Prescribing Information

Velcade® ▼ 3.5 mg powder for solution for injection

ACTIVE INGREDIENT

Bortezomib

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

INDICATION(S)

Monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are not suitable for bone marrow transplantation. In combination with melphalan and prednisolone for the treatment of previously untreated multiple myeloma patients who are not eligible for high-dose chemotherapy with bone marrow transplant.

DOSAGE & ADMINISTRATION

Adults and Elderly

Starting dose 1.3mg/m² body surface area. **Monotherapy:** twice weekly for two weeks followed by a 10-day rest period. **Combination therapy:** administered in combination with oral melphalan (9mg/m²) and prednisolone (60mg/m²) for nine 6-week treatment cycles. Refer to SmPC for dose management. Reconstituted solution given as 3-5 second IV bolus. Treatment must be withheld at the onset of any Grade 3 non-haematological or Grade 4 haematological toxicities (excluding neuropathy). Once the symptoms of the toxicity have resolved, treatment can be re-initiated at a 25% reduced dose. **Children:** Not applicable. **Renal and Hepatic Impairment:** See precautions.

CONTRAINDICATIONS

Hypersensitivity to bortezomib, boron or any of the excipients.

Severe hepatic impairment. Acute diffuse infiltrative pulmonary and pericardial disease.

SPECIAL WARNINGS & PRECAUTIONS

Monitor complete blood counts. Gastrointestinal toxicity is very common, monitor closely. Peripheral neuropathy is common and requires careful monitoring. Patients should undergo neurological evaluation and possible dose modification. Special care of patients with risk factors for seizures. Caution is advised when history of syncope on receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Development or exacerbation of congestive heart failure, QT prolongation. Monitor closely patients with cardiac risk factors and those with renal impairment. Rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology eg pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS). A baseline pretreatment chest radiograph is recommended. In event of new or worsening pulmonary symptoms perform prompt diagnostic evaluation and treat appropriately. Consider benefit/risk ratio before continuing Velcade therapy. Immunocomplex-mediated reactions eg serum sickness, polyarthritis with rash, proliferative glomerulonephritis: discontinue if severe. Extreme caution in patients with hepatic impairment. Patients with high pretreatment tumour burden are at risk of tumour lysis syndrome; monitor closely. Caution in patients with amyloidosis. Monitor patients closely when given concomitant CYP3A4-inhibitors or CYP3A4-inducing medicinal products. Exercise caution when combined with CYP3A4- or CYP2C19 substrates.

SIDE EFFECTS

Herpes zoster (**consider antiviral prophylaxis**), respiratory tract infections, candidal infection, herpes simplex, herpes meningoencephalitis, septic shock, ophthalmic herpes, pneumonia, catheter related infection, gastroenteritis, pleural infection and effusion; tumour lysis syndrome; thrombocytopenia, anaemia, neutropenia, leukopenia, lymphopenia, lymphadenopathy, pancytopenia, haemolytic anaemia, febrile neutropenia, thrombocytopenic purpura; hypersensitivity, immunocomplex mediated hypersensitivity, angioedema, potentially immunocomplex-mediated reactions (serum-sickness-type reaction, polyarthritis with rash, proliferative glomerulonephritis); inappropriate antidiuretic hormone (ADH) secretion; decreased appetite, dehydration, hyperglycaemia, electrolyte imbalance; confusion, depression, insomnia, anxiety, mental status changes; polyneuropathy, peripheral neuropathy, peripheral sensory neuropathy, encephalopathy, headache, dizziness (excl vertigo), dysgeusia, dysaesthesia, paraesthesia, hypoaesthesia, tremor, syncope, autonomic neuropathy, convulsions, intra-cranial and sub-arachnoid haemorrhage; vision blurred, eye pain, conjunctivitis, eye haemorrhage, photophobia; vertigo, tinnitus, deafness; tachycardia, supraventricular



tachycardia, arrhythmia, ventricular hypokinesia, atrial fibrillation, cardiac arrest/ failure, acute pulmonary oedema, angina unstable, atrioventricular block complete, cardiac tamponade, pericarditis, cardiogenic shock, myocardial infarction, sinus arrest; hypotension, hypertension, pulmonary hypertension, phlebitis, haematoma, cerebral haemorrhage; pneumonitis, interstitial pneumonia, acute respiratory distress syndrome (ARDS), acute diffuse infiltrative pulmonary disease, pulmonary alveolar haemorrhage, pulmonary embolism, peripheral embolism, dyspnoea, epistaxis, rhinorrhoea, cough, respiratory alkalosis or arrest, tachypnoea; ischemic colitis, gastrointestinal disorders, nausea, diarrhoea, vomiting, constipation, hiccups, mouth ulceration, pharyngolaryngeal pain, dry mouth, ileus paralytic, acute pancreatitis; hepatitis, liver failure, hypoproteinaemia, hepatic haemorrhage; rash, pruritus, erythema, sweating increased, night sweats, periorbital oedema, urticaria, eczema, alopecia, dry skin, Stevens-Johnson Syndrome, toxic epidermal necrolysis; myalgia, muscle cramps, muscle weakness, musculoskeletal pain, pain in limb, arthralgia, back pain, peripheral swelling, bone pain, joint stiffness/swelling; renal impairment & failure, dysuria, haematuria, proteinuria, urinary frequency & hesitation, renal colic, urinary retention; fatigue, pyrexia, asthenia, weakness, rigors, malaise, influenza-like illness, chest pain, pain, oedema, lethargy, mucosal inflammation & haemorrhage, neuralgia, weight decreased, cachexia, liver function tests abnormal, blood lactate dehydrogenase increased.

Refer to SmPC for other side effects.

PREGNANCY

Not fully established. Use effective contraceptive measures during treatment and for 3 months following.

LACTATION

Not recommended.

INTERACTIONS

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir) and CYP3A4-inducers (e.g. rifampicin). *In vitro* studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. No clinically relevant interaction between melphalan-prednisolone and Velcade. In clinical trials, hypo/hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics.

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Key Opinions in Medicine

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