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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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## Bortezomib Plus Melphalan and Prednisone Compared With Melphalan and Prednisone in Previously Untreated Multiple Myeloma: Updated Follow-Up and Impact of Subsequent Therapy in the Phase III VISTA Trial

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### A B S T R A C T

#### Purpose

The purpose of this study was to confirm overall survival (OS) and other clinical benefits with bortezomib, melphalan, and prednisone (VMP) versus melphalan and prednisone (MP) in the phase III VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) trial after prolonged follow-up, and evaluate the impact of subsequent therapies.

#### Patients and Methods

Previously untreated symptomatic patients with myeloma ineligible for high-dose therapy received up to nine 6-week cycles of VMP (n = 344) or MP (n = 338).

#### Results

With a median follow-up of 36.7 months, there was a 35% reduced risk of death with VMP versus MP (hazard ratio, 0.653;  $P < .001$ ); median OS was not reached with VMP versus 43 months with MP; 3-year OS rates were 68.5% versus 54.0%. Response rates to subsequent thalidomide- (41% v 53%) and lenalidomide-based therapies (59% v 52%) appeared similar after VMP or MP; response rates to subsequent bortezomib-based therapy were 47% versus 59%. Among patients treated with VMP (n = 178) and MP (n = 233), median survival from start of subsequent therapy was 30.2 and 21.9 months, respectively, and there was no difference in survival from salvage among patients who received subsequent bortezomib, thalidomide, or lenalidomide. Rates of adverse events were higher with VMP versus MP during cycles 1 to 4, but similar during cycles 5 to 9. With VMP, 79% of peripheral neuropathy events improved within a median of 1.9 months; 60% completely resolved within a median of 5.7 months.

#### Conclusion

VMP significantly prolongs OS versus MP after lengthy follow-up and extensive subsequent antimyeloma therapy. First-line bortezomib use does not induce more resistant relapse. VMP used upfront appears more beneficial than first treating with conventional agents and saving bortezomib- and other novel agent-based treatment until relapse.

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### INTRODUCTION

In the absence of curative therapy, the goal of treatment for multiple myeloma (MM) is prolonged overall survival (OS). Recent studies have suggested that over the past decade, the introduction of high-dose therapy for eligible patients age  $\leq$  65 years and the novel agents bortezomib, thalidomide, and lenalidomide as rescue therapies has increased OS for patients with MM.<sup>1-3</sup> However, improvements have been less pronounced in elderly patients<sup>1-3</sup>; the unmet need in this

population may be addressed through optimal use of chemotherapy plus novel agents.<sup>1,4-7</sup>

Use of novel agent-based regimens in previously untreated patients ineligible for high-dose therapy has resulted in improved response rates and long-term outcomes, such as time to progression (TTP) and progression-free survival (PFS), compared with conventional regimens.<sup>8</sup> However, analysis of OS is becoming increasingly complicated due to the impact of novel agents as rescue therapies. Indeed, only two<sup>4,9</sup> of five<sup>4,6,9-11</sup> phase III trials of thalidomide plus melphalan and prednisone (MPT)

versus melphalan and prednisone (MP) have shown an OS benefit with MPT. Moreover, it has been suggested that first-line use of novel agents, although initially more effective than conventional chemotherapy regimens, could induce more resistant relapses.<sup>7,12-14</sup> Accordingly, it is of increasing interest to analyze response to subsequent therapies in patients treated upfront with novel agents.

The first report of the international, randomized phase III VISTA trial demonstrated superior efficacy with bortezomib plus melphalan and prednisone (VMP) versus MP in previously untreated patients with MM ineligible for high-dose therapy.<sup>15</sup> Follow-up was limited at first analysis (median, 16.3 months); 12% of patients remained on therapy.<sup>15</sup> We now present updated analyses of OS, time to next therapy (TNT), and treatment-free interval (TFI) to determine whether initial findings of superior efficacy with VMP versus MP are confirmed after prolonged follow-up and more extensive use of subsequent therapy. We also focus on survival from the start of subsequent therapy and response to rescue therapies, to explore whether VMP induced more resistant relapses than MP, and whether VMP used upfront appeared more beneficial than using conventional treatment upfront and saving novel agents until relapse.

## PATIENTS AND METHODS

### Patients and Study Design

VISTA study details have been reported.<sup>15</sup> Briefly, patients with previously untreated MM who were ineligible for high-dose therapy were

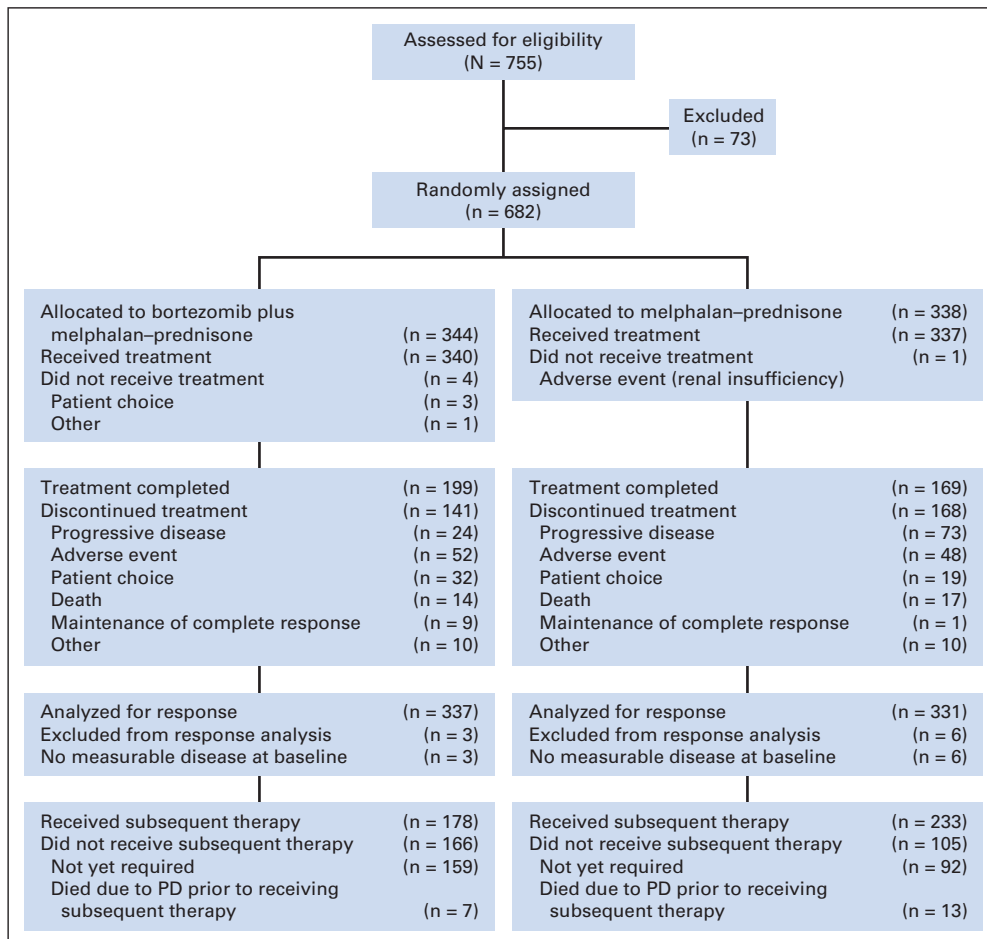
randomly assigned to receive nine 6-week cycles of VMP, comprising bortezomib 1.3 mg/m<sup>2</sup> (days 1, 4, 8, 11, 22, 25, 29, 32, cycles 1 to 4; days 1, 8, 22, 29, cycles 5 to 9) plus melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> (days 1 to 4, all cycles), or MP. Patients with serum creatinine higher than 2 mg/dL or grade ≥ 2 peripheral neuropathy or neuropathic pain by National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 were excluded.

Response and progression were assessed every 3 weeks during treatment and then every 8 weeks until disease progression according to European Group for Blood and Marrow Transplantation criteria,<sup>16</sup> using a central laboratory for M-protein quantification and immunofixation and a validated algorithm. Patients were then followed at least every 12 weeks for survival and subsequent therapy use. Safety was assessed until 30 days postlast dose of study drug; adverse events (AEs) were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0. All patients provided written informed consent. Review boards at all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice.

### Initial and Updated Analyses

VISTA was stopped at the third preplanned interim analysis based on independent data monitoring committee recommendation, as the statistical boundary for the primary end point, TTP, had been crossed. Data cutoff was June 15, 2007; median follow-up was 16.3 months.<sup>15</sup> Eighty patients remained on treatment (47 VMP, 33 MP).<sup>15</sup>

Updated analyses were performed using data collected through March 16, 2009. After the study was stopped, formal centralized collection of M-protein data was stopped and thus subsequent data on response rates, TTP,



**Fig 1.** CONSORT diagram. PD, progressive disease.

and PFS were not updated because the information would not have been based on the same stringent methodology as the initial analysis. Data collection continued for OS, subsequent therapy use, best responses to subsequent therapies as reported by investigators, and safety, including improvement/resolution of AEs (until 30 days post-treatment completion).

### Statistical Analysis

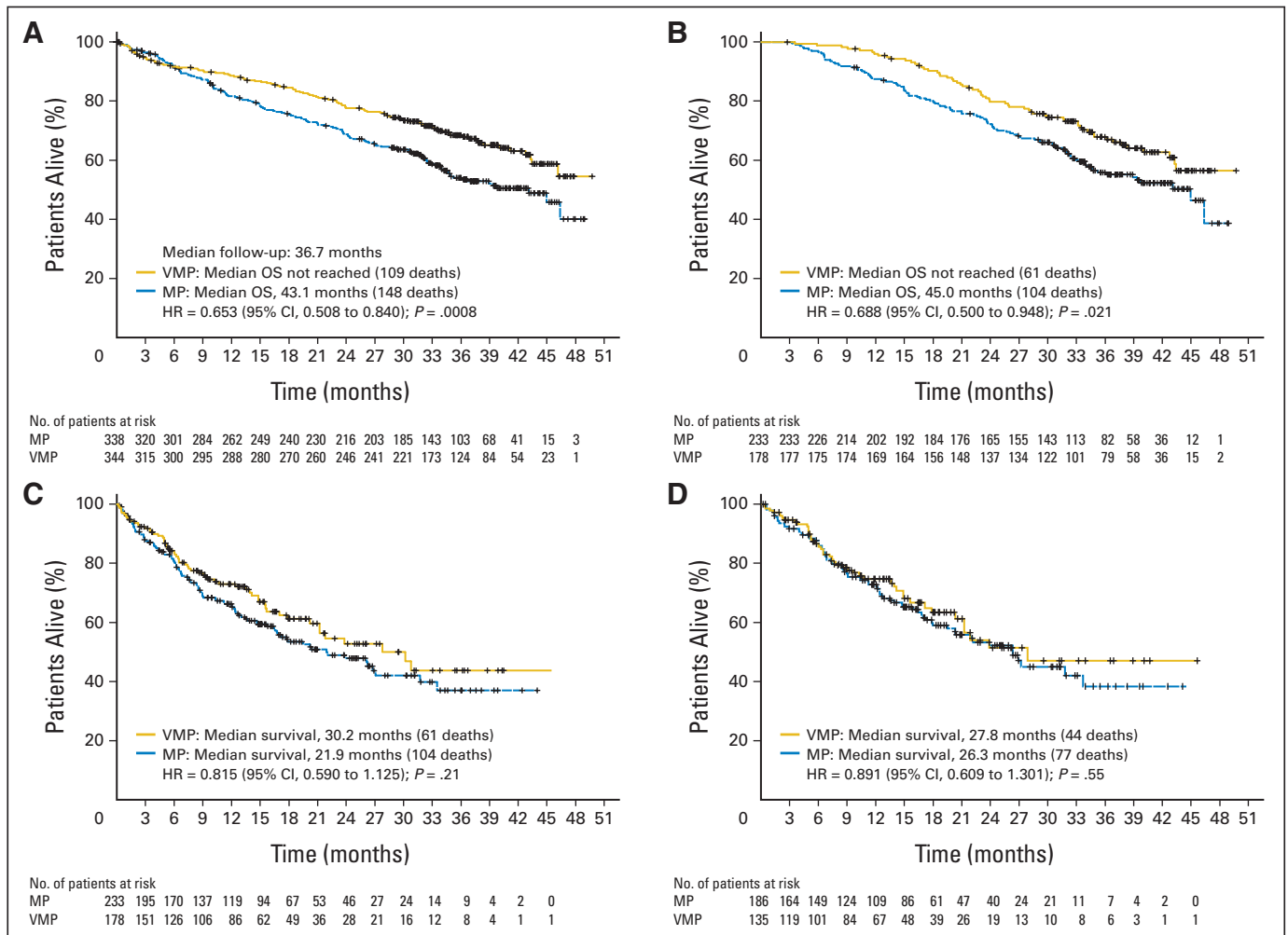
OS (random assignment until death), TNT (random assignment until first dose of subsequent anti-MM therapy), and TFI (last dose of VISTA study drug until first dose of subsequent anti-MM therapy) were analyzed using Kaplan-Meier methodology. Time-to-event data were compared between arms using stratified log-rank tests in intent-to-treat analyses. In posthoc analyses among patients treated with VMP, OS was evaluated within subgroups with/without poor prognostic characteristics, including advanced age, impaired renal function, and high-risk cytogenetics. In exploratory posthoc analyses, survival was evaluated from random assignment and from start of subsequent therapy by arm in patients who had received any subsequent therapy and according to subsequent therapy received. Safety was analyzed in all patients who received at least one dose of study drug. Rates of treatment-emergent AEs were analyzed overall and by treatment cycle.

## RESULTS

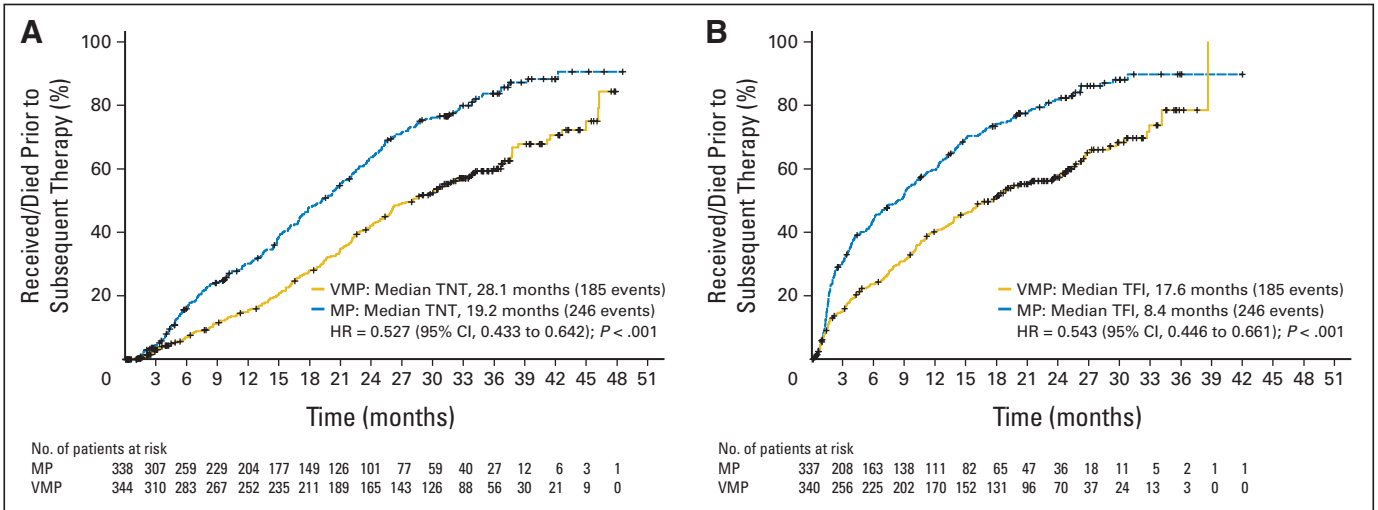
### Patient Characteristics and Disposition

A total of 682 patients were randomly assigned to receive VMP (n = 344) or MP (n = 338). Baseline demographics and disease characteristics were previously reported,<sup>15</sup> and are summarized in Appendix Table A1 (online only). Overall, median age was 71 years, 30% of patients were age  $\geq$  75 years, 34% had International Staging System<sup>17</sup> stage III MM, and 33% had  $\beta_2$ -microglobulin higher than 5.5 mg/L. At the initial analysis, VMP was superior to MP across all efficacy end points, including response rate (71% v 35%), complete response (CR) rate (30% v 4%), TTP (median, 24.0 v 16.6 months; hazard ratio [HR], 0.48;  $P < .001$ ), and OS (HR, 0.61;  $P = .008$ ).<sup>15</sup> Data not updated (see Patients and Methods) are summarized in Appendix Table A2 (online only).

Updated patient disposition at data cutoff for this analysis (March 16, 2009) is shown in Figure 1 (CONSORT). All patients have completed VISTA study treatment. Median number of treatment



**Fig 2.** Overall survival (OS) from random assignment in the bortezomib, melphalan, and prednisone (VMP) and melphalan and prednisone (MP) arms in (A) the overall population (ITT analysis), and (B) only patients randomly assigned to VMP or MP who had received subsequent therapy by data cutoff for the present analysis. Survival from the start of second-line therapy in (C) all patients who had received subsequent therapy, and (D) patients who received any subsequent novel agents. HR, hazard ratio.



**Fig 3.** (A) Time to next therapy (TNT) and (B) treatment-free interval (TFI) with bortezomib, melphalan, and prednisone (VMP) and melphalan and prednisone (MP). HR, hazard ratio.

cycles administered was nine (50 weeks) and eight (48 weeks) in the VMP and MP arms, respectively.

**OS**

After median follow-up of 36.7 months, OS was prolonged with VMP versus MP (HR, 0.653;  $P < .001$ ), with VMP associated with a 35% reduced risk of death. Median OS was not estimable versus 43.1 months in the VMP and MP arms, respectively, with 109 (32%) and 148 (44%) patients having died (Fig 2A); 3-year OS rates were 68.5% versus 54.0%, respectively. The improved OS with VMP versus MP in patient subgroups predefined by age, sex, race,  $\beta_2$ -microglobulin, albumin, region, International Staging System stage, and creatinine clearance is shown in Appendix Figure A1 (online only).

**Subsequent Therapy**

At data cutoff, 178 (52%) and 233 patients (69%) in the VMP and MP arms, respectively, had received subsequent therapy. TNT and TFI with VMP versus MP are shown in Figure 3; median TNT was 28.1 months versus 19.2 months (HR, 0.527;  $P < .001$ ), and median TFI was 17.6 months versus 8.4 months (HR, 0.543;  $P < .001$ ). In the VMP and MP arms, 42.7% and 18.1% of patients, respectively, had a TFI of  $\geq 2$  years.

Novel agents received as part of subsequent anti-MM therapy are summarized in Appendix Table A3 (online only). Among patients who received subsequent therapy in the VMP and MP arms, respectively, 43 (24%) and 116 (50%) received bortezomib, 81 (46%) and 110 (47%) received thalidomide, and 57 (32%) and 30 (13%) received

**Table 1.** Investigator-Reported Best Responses (including for current subsequent therapy if ongoing for  $\geq 3$  months at data cutoff) to Second-Line, Third-Line, and Beyond, and Any Subsequent (second-line and beyond) Bortezomib-, Thalidomide-, and Lenalidomide-Based Therapy in Patients Originally Randomly Assigned to the VMP and MP Arms

Subsequent Therapy and Responses Achieved	Arm by Line											
	VMP					MP						
	2nd		$\geq 3rd$		Any*	2nd		$\geq 3rd$		Any*		
	No.	%	No.	%	No.	%	No.	%	No.	%		
Bortezomib-based therapy (No. with data/No. total)	22/25		17/21		36/43		76/82		49/50		109/116	
CR + PR†	9	41	8	47	17	47	45	59	27	55	64	59
CR†	2	9	0		2	6	6	8	5	10	9	8
Thalidomide-based therapy (No. with data/No. total)	63/71		19/23		73/81		73/84		38/44		97/110	
CR + PR†	23	37	10	53	30	41	34	47	21	55	51	53
CR†	2	3	0		2	3	1	1	4	11	5	5
Lenalidomide-based therapy (No. with data/No. total)	22/26		27/34		46/57		9/10		14/21		23/30	
CR + PR†	16	73	12	44	27	59	6	67	6	43	12	52
CR†	2	9	2	7	4	9	1	11	0		1	4

Abbreviations: VMP, bortezomib, melphalan, and prednisone; MP, melphalan and prednisone; CR, complete response; PR, partial response.  
 \*Patients could have received more than one agent, either within the same combination regimen, as part of consecutive separate regimens within the same line of therapy, or as part of separate regimens within different subsequent lines of therapy. These patients are included in each of the relevant groups.  
 †Percentage response rates calculated using the number of patients with data as the denominator. No. with data represents the numbers of patients for whom the investigators reported the response to subsequent therapy; in each arm, responses to subsequent therapy were unknown or missing for some of the total number of patients who received the subsequent therapy.

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lenalidomide. Investigator-reported best responses to novel agent-based subsequent therapies are summarized in Table 1. Response rates to second-line bortezomib-, thalidomide-, and lenalidomide-based therapies were 41%, 37%, and 73%, respectively, after VMP, and 59%, 47%, and 67%, respectively, after MP; respective response rates to therapies received at third line and beyond were 47%, 53%, and 44% after VMP, and 55%, 55%, and 43% after MP. Efficacy of bortezomib-based re-treatment as second-line therapy in patients randomly assigned to VMP was evaluated according to TFI. Among 16 patients with TFI  $\leq$  12 months, response rate was 25%, including 6% CR. Among nine patients with TFI longer than 12 months, response rate (in seven with response reported) was 71%, including 14% CR.

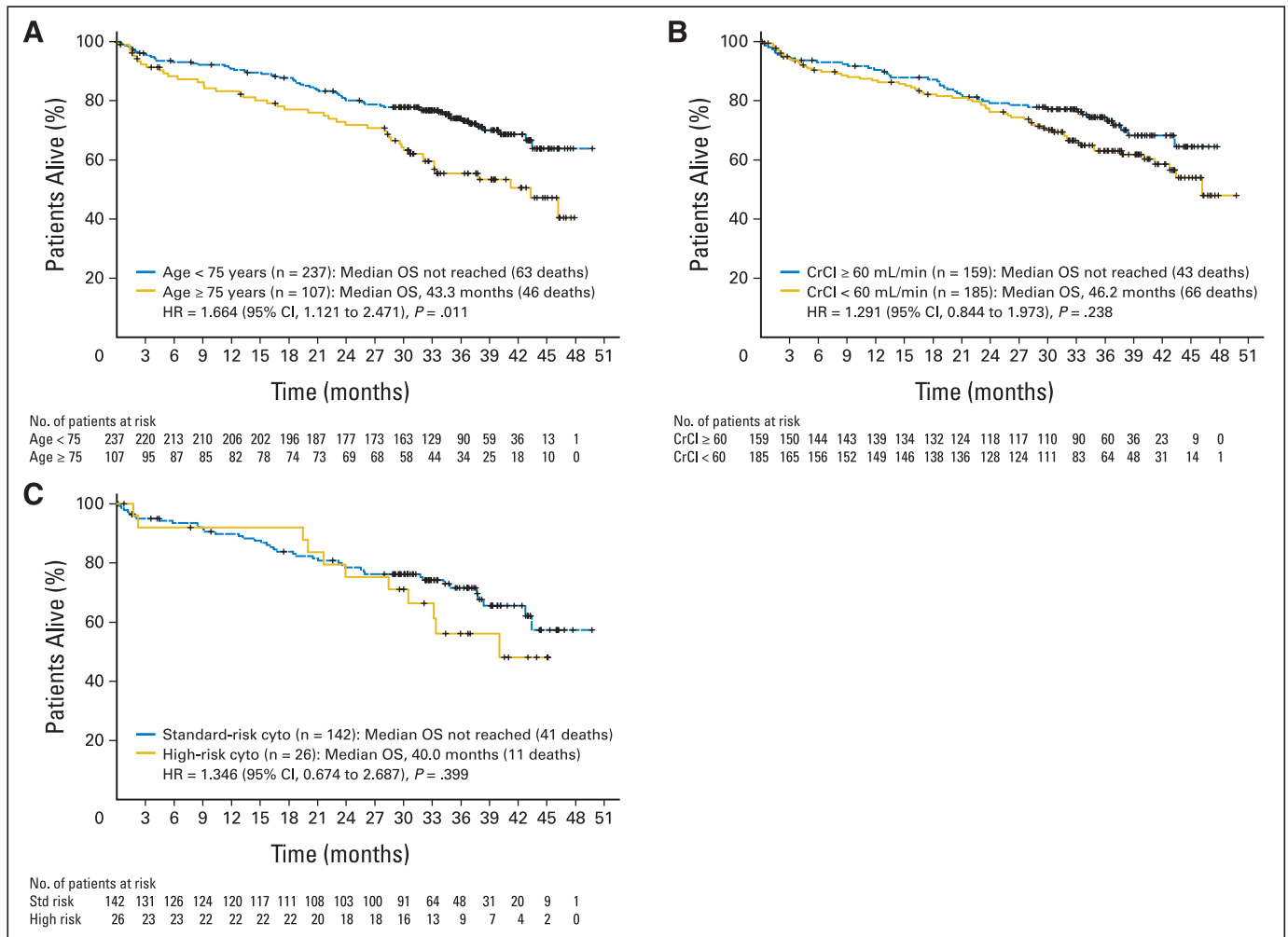
Figure 2B shows OS from initial random assignment among patients treated with VMP and MP who received subsequent therapy (HR, 0.688;  $P = .021$ ); 3-year OS rates were 67.9% and 55.9%, respectively. The OS advantage with VMP was also seen versus the subgroup of patients treated with MP who received bortezomib as second-line therapy (data not shown). Median survival from start of subsequent therapy was 30.2 and 21.9 months after VMP and MP, respectively (Fig 2C; HR, 0.815;  $P = .21$ ). Notably, survival from start of subse-

quent therapy was similar after VMP versus MP among patients who received any novel agents as subsequent therapy (Fig 2D; median 27.8 v 26.3 months; HR, 0.891;  $P = .55$ ) and among patients who received subsequent thalidomide and lenalidomide but no bortezomib (median 27.8 months v not reached; HR, 0.766;  $P = .35$ ).

**VMP Subgroup Analyses**

Within the VMP arm, OS was longer among patients age younger than 75 versus  $\geq$  75 years (HR, 1.664;  $P = .011$ ; 3-year OS: 74.1% v 55.5%; Fig 4A). By contrast, there were no statistically significant differences although there were trends to longer OS among patients with creatinine clearance  $\geq$  60 versus fewer than 60 mL/min (HR, 1.291;  $P = .238$ ; 3-year OS: 74.5% v 63.1%; Fig 4B), and patients with standard risk versus high-risk cytogenetics (HR, 1.346;  $P = .399$ ; 3-year OS 71.6% v 56.1%; Fig 4C).

Novel agents received as part of subsequent therapy according to age, baseline creatinine clearance, and cytogenetics are summarized in Appendix Table A4 (online only). Survival from start of subsequent therapy appeared shorter among patients with creatinine



**Fig 4.** Overall survival (OS) from random assignment in the bortezomib, melphalan, and prednisone arm in patients (A) age  $\leq$  75 and older than 75 years, (B) with creatinine clearance (CrCl)  $\geq$  60 and shorter than 60 mL/min, (C) with standard-risk (std) and high-risk (t(4;14), t(14;16), del(17p)) cytogenetics (cyto) by fluorescence in situ hybridization. HR, hazard ratio.

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**Table 2.** Grade 3 and 4 Adverse Events Occurring in  $\geq 5\%$  of Patients in Either the VMP or MP Arm

Adverse Event	Arm by Grade (%)			
	VMP (n = 340)		MP (n = 337)	
	3	4	3	4
Neutropenia	29	11	23	15
Thrombocytopenia	20	18	16	15
Anemia	16	3	20	8
Leukopenia	21	3	16	4
Lymphopenia	14	6	9	2
Peripheral sensory neuropathy	13	< 1	0	0
Neuralgia	8	1	< 1	0
Fatigue	7	1	2	0
Diarrhea	7	1	1	0
Pneumonia	5	2	4	1
Hypokalemia	6	1	2	1
Asthenia	6	< 1	3	0

Abbreviations: VMP, bortezomib, melphalan, and prednisone; MP, melphalan and prednisone.

**Table 3.** Tolerability of VMP and MP Therapy by Treatment Cycle

Parameter	Cycle (%)					
	VMP			MP		
	All	1-4	5-9	All	1-4	5-9
No. of patients	340	340	249	337	337	234
Any treatment-emergent adverse event	99	99	91	97	95	88
Grade 1 maximum severity	1	NA	NA	3	NA	NA
Grade 2 maximum severity	8	NA	NA	14	NA	NA
Any grade $\geq 3$ treatment-emergent adverse event	91	85	62	80	66	63
Grade 3 maximum severity	53	NA	NA	44	NA	NA
Grade 4 maximum severity	29	NA	NA	28	NA	NA
Any serious adverse event	46	40	14	36	29	16
Discontinuation of regimen because of adverse events	15*	12*	5*	14	8	7

Abbreviations: VMP, bortezomib, melphalan, and prednisone; MP, melphalan and prednisone; NA, not assessable.  
\*Data represent discontinuation of all treatment; in addition, 19% of VMP patients discontinued bortezomib but remained on MP, 15% and 4% during cycles 1-4 and 5-9, respectively.

clearance shorter than 60 versus  $\geq 60$  mL/min who received subsequent thalidomide and lenalidomide but no bortezomib (Appendix Fig A2A, online only); no difference was apparent among the small number of patients who received subsequent bortezomib but no thalidomide and lenalidomide (Appendix Fig A2B). TNT was similar between patients with high-risk versus standard-risk cytogenetics (median 24.1 v 27.4 months; HR, 1.478;  $P = .17$ ); survival from start of subsequent therapy appeared similar between cytogenetic risk groups among patients who received any subsequent novel agent-based therapy (Appendix Fig A2C) but substantially shorter in two high-risk (6 and 15.5 months) versus 17 standard-risk patients (median, 30.8 months) who received no subsequent novel agents.

### Safety

Safety profiles were similar to those reported at the initial analysis.<sup>15</sup> Rates of on-study deaths were similar between the VMP (n = 19; 6%) and MP (n = 14; 4%) arms, including 2% treatment-related deaths on each arm. Rates of treatment discontinuation due to AEs remained similar (15%/14% in the VMP/MP arms). Grade 3/4 AEs that occurred at an incidence of  $\geq 5\%$  in either arm are presented in Table 2.

The rate of peripheral neuropathy with VMP was almost identical to that reported at the initial analysis.<sup>15</sup> After prolonged follow-up, 79% of peripheral neuropathy events had improved/resolved within a median of 1.9 months, while 60% completely resolved within a median of 5.7 months. Among 159 patients who had peripheral neuropathy while receiving VMP, 21 (13%), 36 (23%), and 39 (25%) have received subsequent bortezomib-, thalidomide-, and lenalidomide-based therapy, respectively, compared with 22 (12%), 45 (24%), and 18 (10%), respectively, of the 185 patients who did not report peripheral neuropathy. Among 21 patients who had peripheral neuropathy during VMP therapy and subsequently received bortezomib-based therapy, 16 (76%) had at least one event improved/resolved, including 12 (57%) with at least one event resolved, by the start of subsequent therapy.

VMP and MP safety profiles by treatment cycle are summarized in Table 3. Rates of AEs were higher with VMP versus MP during cycles 1 to 4, but similar during cycles 5 to 9. Rates of AEs, grade  $\geq 3$  AEs, serious AEs, and discontinuations due to AEs in the VMP arm

were lower during cycles 5 to 9 compared with cycles 1 to 4. In the MP arm, rates of grade  $\geq 3$  AEs and discontinuations due to AEs were similar in cycles 1 to 4 and cycles 5 to 9.

## DISCUSSION

The results of this updated analysis of the international phase III VISTA trial after prolonged follow-up (median, 36.7 months) confirm that VMP results in significantly longer OS compared with MP in previously untreated patients with MM who are ineligible for high-dose therapy. This OS benefit was seen consistently across patient subgroups predefined by baseline characteristics, including age, disease stage, and creatinine clearance.

This confirmed survival advantage represents an important finding, as an OS benefit has not been consistently reported in other studies of novel agent-based regimens versus MP. For example, an OS benefit was reported in two studies of MPT versus MP by the Intergroupe Francophone du Myélome,<sup>4,9</sup> but not in three other similar phase III studies.<sup>6,10,11</sup> One reason suggested for the lack of OS benefit with MPT was the confounding impact of subsequent therapies containing novel agents in patients receiving MP upfront.<sup>6,11</sup>

However, in VISTA, the OS benefit with VMP versus MP was seen both overall and in an analysis restricted to patients who had received subsequent therapy, despite 50% of patients treated with MP being rescued with bortezomib-based therapy in the relapsed setting. Indeed, this benefit was retained with VMP versus MP followed by bortezomib as second-line therapy. Thus, our results indicate that using bortezomib-based treatment in the first-line setting provides greater survival benefit to patients compared with the approach of administering first-line treatment with conventional agents and saving bortezomib- and other novel agent-based treatment for salvage.

Patients receiving VMP experienced greater clinical benefit versus those receiving MP in terms of TNT and TFL. Among patients who had received subsequent therapy, taking into consideration potential differences in the order in which subsequent therapies were received, as well as the possible confounding factor of the different proportions

of patients on each arm who had received subsequent therapy, response rates to subsequent thalidomide- and lenalidomide-based therapies appeared similar between arms. Furthermore, re-treatment with bortezomib-based therapies after VMP was effective; the 47% response rate reflects similar findings in studies of bortezomib-based re-treatment in relapsed MM.<sup>18-22</sup> As might be expected, the response rate to subsequent bortezomib-based therapies appeared somewhat higher in bortezomib-naïve patients after MP (59%). Survival from start of subsequent therapy was not shorter, and may even be longer, among patients randomly assigned to VMP versus MP (median 30.2 v 21.9 months). Importantly, there was no difference between arms in survival from start of subsequent therapy among patients who received any subsequent novel agents. Our findings indicate that patients relapsing after bortezomib-based therapy are not intrinsically more resistant to subsequent therapies, and can be as successfully treated with subsequent immunomodulator-based therapies, compared with those relapsing after traditional chemotherapy with MP; VMP treatment does not appear to select a more resistant clone.

Within the VMP arm, OS was longer among patients younger than 75 versus  $\geq 75$  years, reflecting the expected adverse impact on survival of advanced age. Nonstatistically significant differences in OS were seen among patients treated with VMP with or without renal impairment and high-risk cytogenetics. Notably, OS curves appeared similar until approximately 24 to 28 months (median TTP/TNT), and subsequently appeared to show greater divergence with a trend to shorter OS for patients with adverse characteristics. Regarding this apparent impact of renal impairment, our findings indicated that among patients treated with VMP who received subsequent therapy including thalidomide and lenalidomide but not bortezomib, survival from start of subsequent therapy was longer in patients with creatinine clearance  $\geq 60$  versus lower than 60 mL/min. By contrast, survival did not appear affected by renal function among patients who received subsequent bortezomib but not thalidomide and lenalidomide. However, these are retrospective analyses, and should thus be interpreted with caution. Regarding outcomes among patients treated with VMP with high-risk cytogenetics, we observed similar survival from start of subsequent therapy among 15 high-risk and 57 standard-risk patients who received novel agent-based rescue therapies. Thus, a possible interpretation of the trend toward shorter OS among patients with high-risk versus standard-risk cytogenetics is that there was a trend toward earlier receipt of subsequent therapy in high-risk patients, and that two of 17 high-risk patients were not exposed to novel agents after relapse and had notably poor survival from start of subsequent therapy. However, the small number of patients treated with VMP with high-risk cytogenetics precludes drawing any firm conclusions. At the initial analysis, response rates and TTP with VMP were similar among patients with or without these adverse characteristics.<sup>15</sup> Overall, our findings reflect those from a pilot phase I to II study of VMP<sup>23</sup> and preliminary data from other phase III studies of modified VMP regimens,<sup>24,25</sup> in which high-risk cytogenetics did not affect response rates,<sup>23-25</sup> TTP,<sup>23</sup> or PFS.<sup>25</sup> Similarly, high-risk cytogenetics did not affect response rates with other bortezomib-based regimens in previously untreated patients with MM.<sup>26-29</sup>

At this updated analysis, after completion of therapy among 80 patients who were ongoing at the initial analysis, the overall safety profiles of VMP and MP were essentially unchanged. VMP was generally well-tolerated, with manageable toxicities. Our analysis of treatment-emergent AEs by treatment cycle demonstrated that toxicities associated with VMP were substantially lower during cycles 5 to 9

versus cycles 1 to 4 and similar to those associated with MP. Thus, while initial substantial tumor-burden reduction with twice-weekly bortezomib during cycles 1 to 4 was associated with somewhat more frequent toxicities with VMP versus MP, tolerability was improved and comparable to MP during weekly bortezomib maintenance (cycles 5 to 9), with improved responses and an increased CR rate from the end of cycle 4.<sup>30</sup> Regimens using weekly bortezomib dosing schedules are currently under investigation<sup>24,25</sup> and showing a clear reduction in toxicity, but longer follow-up is needed to confirm if efficacy is maintained.

After prolonged follow-up, the rate of improvement or resolution of peripheral neuropathy events on the VMP arm was 79%, demonstrating that this toxicity is reversible in the majority of cases. Indeed, 60% of events had resolved completely to baseline by data cutoff, within a median of 5.7 months. Our findings are supported by data on reversibility of peripheral neuropathy with single-agent bortezomib in first-line<sup>31</sup> and relapsed<sup>32</sup> MM.

In conclusion, this updated analysis of VISTA supports the strategy of using bortezomib-based treatment as first-line therapy instead of as salvage after upfront conventional therapy. Our results confirm the significant survival benefit and the other clinical benefits of TNT and TFI with VMP versus MP. The survival benefit was demonstrated even with the use of subsequent novel agent-based therapies in patients treated with MP alone upfront. Indeed, salvage therapies appeared similarly effective in patients initially randomly assigned to VMP or MP, demonstrating that the use of bortezomib upfront does not preclude the successful use of novel agents at relapse. Moreover, postrelapse survival even appeared longer after VMP, indicating that first-line bortezomib use does not induce more resistant relapse.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## REFERENCES

- Brenner H, Gondos A, Pulte D: Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood* 111:2521-2526, 2008
- Kastritis E, Zervas K, Symeonidis A, et al: Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): An analysis of the Greek Myeloma Study Group (GMSG). *Leukemia* 23:1152-1157, 2009
- Kumar SK, Rajkumar SV, Dispenzieri A, et al: Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 111:2516-2520, 2008
- Facon T, Mary JY, Hulin C, et al: Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): A randomised trial. *Lancet* 370:1209-1218, 2007
- Mateos MV, Hernandez JM, Hernandez MT, et al: Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Results of a multicenter phase 1/2 study. *Blood* 108:2165-2172, 2006
- Palumbo A, Bringhen S, Liberati AM, et al: Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: Updated results of a randomized, controlled trial. *Blood* 112:3107-3114, 2008
- San-Miguel J, Harousseau JL, Joshua D, et al: Individualizing treatment of patients with myeloma in the era of novel agents. *J Clin Oncol* 26:2761-2766, 2008
- Palumbo A, Rajkumar SV: Treatment of newly diagnosed myeloma. *Leukemia* 23:449-456, 2009
- Hulin C, Facon T, Rodon P, et al: Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 Trial. *J Clin Oncol* 27:3664-3670, 2009
- Waage A, Gimsing P, Juliusson G, et al: Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: A placebo controlled randomised phase 3 trial. *Blood* 110:32a, 2007 (suppl); abstr 78
- Wijermans P, Schaafsma M, Van Norden Y, et al: Melphalan + prednisone versus melphalan + prednisone + thalidomide in induction therapy for multiple myeloma in elderly patients: Final analysis of the Dutch Cooperative Group HOVON 49 study. *Blood* 112:241, 2008 (suppl); abstr 649
- Barlogie B, Tricot G, Anaissie E, et al: Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 354:1021-1030, 2006
- Barlogie B, Pineda-Roman M, van Rhee F, et al: Thalidomide arm of total therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood* 112:3115-3121, 2008
- Morgan GJ, Jackson GH, Davies FE, et al: Maintenance thalidomide may improve progression free but not overall survival; results from the Myeloma IX maintenance randomisation. *Blood* 112:245, 2008 (suppl); abstr 656
- San Miguel JF, Schlag R, Khuageva NK, et al: Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 359:906-917, 2008
- Bladé J, Samson D, Reece D, et al: Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation: Myeloma Subcommittee of the EBMT. *Br J Haematol* 102:1115-1123, 1998
- Greipp PR, San Miguel J, Durie BG, et al: International staging system for multiple myeloma. *J Clin Oncol* 23:3412-3420, 2005
- Conner TM, Doan QD, Walters IB, et al: An observational, retrospective analysis of retreatment with bortezomib for multiple myeloma. *Clin Lymphoma Myeloma* 8:140-145, 2008
- Hrusovsky I, Emmerich B, von Rohr A, et al: Bortezomib retreatment in relapsed multiple myeloma (MM): Results from a binational, multicenter retrospective survey. *Blood* 112:957, 2008 (suppl); abstr 2775
- Petrucci MT, Blau IW, Corradini P, et al: Efficacy and safety of re-treatment with bortezomib (Velcade®) in patients with multiple myeloma: Results from a prospective international phase II trial. *Blood* 112:1264, 2008 (suppl); abstr 3690
- Rubio-Martinez A, Recasens V, Soria B, et al: Response to re-treatment on relapse multiple myeloma patients previously treated with bortezomib. *Haematologica* 93:261, 2008 (suppl); abstr 649
- Wolf J, Richardson PG, Schuster M, et al: Utility of bortezomib retreatment in relapsed or refractory multiple myeloma patients: A multicenter case series. *Clin Adv Hematol Oncol* 6:755-760, 2008
- Mateos MV, Hernandez JM, Hernandez MT, et al: Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Updated time-to-events results and prognostic factors for time to progression. *Haematologica* 93:560-565, 2008
- Mateos MV, Oriol A, Martinez J, et al: Bortezomib (Velcade)-melphalan-prednisone (VMP) versus Velcade-thalidomide-prednisone (VTP) in elderly untreated multiple myeloma (MM) patients. *Haematologica* 94:190, 2009 (suppl); abstr 471
- Palumbo A, Bringhen S, Rossi D, et al: Bortezomib, melphalan, prednisone and thalidomide (VMPT) versus bortezomib, melphalan and prednisone (VMP) in elderly newly diagnosed myeloma patients: A prospective, randomized, phase III study. *Haematologica* 94:190-191, 2009 (suppl); abstr 472
- Cavo M, Tacchetti P, Patriarca F, et al: Superior complete response rate and progression-free survival after autologous transplantation with up-front Velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma. *Blood* 112:65, 2008 (suppl); abstr 158
- Harousseau JL, Mathiot C, Attal M, et al: Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial. *J Clin Oncol* 26:455s, 2008 (suppl); abstr 8505
- Rosiñol L, Oriol A, Mateos MV, et al: Phase II pethema trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: Efficacy and clinical implications of tumor response kinetics. *J Clin Oncol* 25:4452-4458, 2007
- Richardson P, Lonial S, Jakubowiak A, et al: Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: Encouraging efficacy in high risk groups with updated results of a phase I/II study. *Blood* 112:41, 2008 (suppl); abstr 92
- Palumbo A, Schlag R, Khuageva N, et al: Prolonged therapy with bortezomib plus melphalan-prednisone (VMP) results in improved quality and duration of response in the phase III VISTA study in previously untreated multiple myeloma (MM). *Haematologica* 93:83, 2008 (suppl); abstr 207
- Richardson PG, Xie W, Mitsiades C, et al: Single-agent bortezomib in previously untreated multiple myeloma: Efficacy, characterization of peripheral neuropathy, and molecular correlates of response and neuropathy. *J Clin Oncol* 27:3518-3525, 2009
- Richardson PG, Sonneveld P, Schuster MW, et al: Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: Impact of a dose-modification guideline. *Br J Haematol* 144:895-903, 2009