ORIGINAL REPORT

Persistent Overall Survival Benefit and No Increased Risk of Second Malignancies With Bortezomib-Melphalan-Prednisone Versus Melphalan-Prednisone in Patients With Previously Untreated Multiple Myeloma

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A B S T R A C T

Purpose
This final analysis of the phase III VISTA trial (Velcade As Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone) was conducted to determine whether the overall survival (OS) benefit with bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) in patients with myeloma who were ineligible for transplantation was maintained after 5 years of follow-up and to explore the risk of second primary malignancies.

Patients and Methods
In all, 682 patients received up to nine 6-week cycles of VMP or MP and were then observed every 12 weeks or less. Data on second primary malignancies were collected by individual patient inquiries at all sites from 655 patients.

Results
After median follow-up of 60.1 months (range, 0 to 74 months), there was a 31% reduced risk of death with VMP versus MP (hazard ratio [HR], 0.695; $P < .001$; median OS 56.4 v 43.1 months). OS benefit with VMP was seen across prespecified patient subgroups (age $\geq$ 75 years, stage III myeloma, creatinine clearance < 60 mL/min). Sixty-three percent of VMP patients and 73% of MP patients had received subsequent therapy. Time to next therapy (median, 30.7 v 20.5 months; HR, 0.557; $P < .001$) was longer with VMP than with MP. Among patients who received subsequent therapies, survival from start of subsequent therapy was similar following VMP (median, 28.1 months) or MP (median, 26.8 months; HR, 0.914). Following VMP/MP, incidence proportions of hematologic malignancies (1%/1%) and solid tumors (5%/3%) and exposure-adjusted incidence rates (0.017/0.013 per patient-year) were similar and were consistent with background rates.

Conclusion
VMP resulted in a significant reduction in risk of death versus MP that was maintained after 5 years' follow-up and despite substantial use of novel-agent-based salvage therapies. There is no emerging safety signal for second primary malignancies following VMP.

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INTRODUCTION

Prolonging overall survival (OS) remains the ultimate goal of treatment for multiple myeloma (MM) in the absence of curative therapy.[1,2] However, particularly for regimens in the first-line setting, demonstrating improved OS is challenging because of the availability of multiple highly active treatment options for subsequent therapy on relapse or progression.[3,4] Population-based analyses have demonstrated that median OS has improved over the past two decades, and it has been associated with the use

of autologous stem-cell transplantation for younger patients and the use of novel agents such as bortezomib, thalidomide, and lenalidomide.[5-9] Notably, some phase III trials in patients ineligible for transplantation[10-20] have reported prolonged OS with regimens based on novel agents versus previous standards of care.[13,14,19] A frequent criticism of studies showing positive results with experimental treatments is that data are preliminary, notably for OS. This is of particular relevance in MM, for which it could be argued that conventional, less-expensive first-line treatment followed by optimized rescue

therapies may prove equivalent to the first-line use of novel regimens. Thus, confirmation of benefit after long-term follow-up is essential.

Another important issue is the risk of developing second primary malignancies because patients are living longer from time of diagnosis.[21] Population studies[22-25] and data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program[26] have shown that patients with MM have an increased risk of developing specific second primary malignancies following their initial diagnosis, most notably, acute myeloid leukemia,[26] associated either with the disease itself or with the use of some specific agents.[20,24,27-34] As demonstrated by SEER data, the risk of developing these malignancies may increase with time from diagnosis.[26] Clearly, this issue is of increasing importance for patients with MM, particularly in the context of prolonged OS.

Per protocol, we conducted a final updated OS analysis of the international, phase III VISTA trial (Velcade As Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone) after a median follow-up of 5 years. VISTA compared efficacy and safety of bortezomib-melphalan-prednisone (VMP) with melphalan-prednisone (MP) in previously untreated patients with MM who were ineligible for transplantation. To the best of our knowledge, this report represents the longest median follow-up in phase III trials of novel agents in combination with MP in this population.[10-18,20] Data from the initial analysis, with median follow-up of 16.3 months, showed that VMP was superior to MP across all efficacy end points, including response rates, time to progression (TTP), and OS.[11] An updated analysis, with median follow-up of approximately 3 years, demonstrated a continued significant OS benefit with VMP.[10] This final analysis was therefore conducted to determine whether the significant OS benefit was maintained after 5 years, after extensive use of subsequent therapies based on novel agents as salvage therapies, and to explore for the first time the risk of second primary malignancies with long-term use of bortezomib in VMP.

PATIENTS AND METHODS

Patients and Study Design

VISTA study details have been reported.[10,11] Briefly, 682 patients with previously untreated MM who were ineligible for high-dose therapy were enrolled at 151 sites in 22 countries in Europe, North America, South America, and Asia. Eligible patients were age ≥ 18 years and had symptomatic, measurable disease; exclusion criteria included grade ≥ 2 peripheral neuropathy or neuropathic pain and a serum creatinine level of more than 2 mg/dL. Review boards at all participating institutions approved the study, which was conducted according to International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patients were randomly assigned 1:1 to receive nine 6-week cycles of VMP (n = 344; bortezomib 1.3 mg/m² per day on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9, with melphalan 9 mg/m² and prednisone 60 mg/m² per day on days 1 through 4 of all cycles) or MP alone (n = 338). The primary end point was TTP. Secondary end points included response rates, OS, and safety/tolerability; additional end points included time to next therapy (TTNT; from random assignment to start of subsequent anti-MM treatment) and treatment-free interval (TFI; from the last dose of study drug to the start of subsequent treatment). Response and progression were assessed according to European Group for Blood and Bone Marrow Transplantation (EBMT) criteria[35] by using central laboratory M-protein assessment. Central laboratory assessment was stopped following the third preplanned interim analysis[10,11]; consequently response, TTP, and progression-free survival (PFS) data could not be updated beyond this initial

report (median follow-up, 16.3 months) according to the same stringency because centralized M-protein assessment was no longer available.

Per protocol, patients were observed at least every 12 weeks for up to 4.5 years after the last-patient-in date for survival and subsequent therapy; data cutoff was March 24, 2011. Data on second primary malignancies were collected by individual patient inquiries at all study sites during February 2011 from 655 patients (96%).

Statistical Analysis

OS was analyzed by using Kaplan-Meier methodology, and TTNT and TFI were analyzed by using cumulative incidence methodology. Data were compared between arms by using stratified log-rank tests, and hazard ratios (HRs) with 95% CIs were calculated. OS was compared between arms and within arms in prespecified patient subgroups defined by age, sex, race, region, baseline β_2-microglobulin, baseline albumin, International Staging System (ISS) disease stage,[36] and renal function. OS was also evaluated in patients with documented high-risk cytogenetics such as t(4;14), t(14;16), and del(17p). OS was compared according to best response (by EBMT criteria), overall and by treatment arm, by using multivariate Cox regression with time-dependent covariates that incorporated response, with adjustment for baseline β_2-microglobulin, baseline albumin, and region as stratification factors, plus age, sex, race, type of MM, baseline Karnofsky performance status, and number of bone lesions at baseline as covariates. OS and survival from start of subsequent therapy were also evaluated in patients who had received subsequent therapies, and OS was compared between all patients on the VMP arm and patients on the MP arm who had not yet relapsed, received salvage therapy with bortezomib, or died without receiving subsequent therapy.

For analyses of second primary malignancies, incidence proportions and exposure-adjusted incidence rates were calculated, plus relative risks and 95% CIs. Exposure was defined as total duration of follow-up in each patient from start of treatment to the time of reporting occurrence of second primary malignancy. Incidence rate was calculated by dividing total number of second primary malignancies by duration of exposure in patient-years.
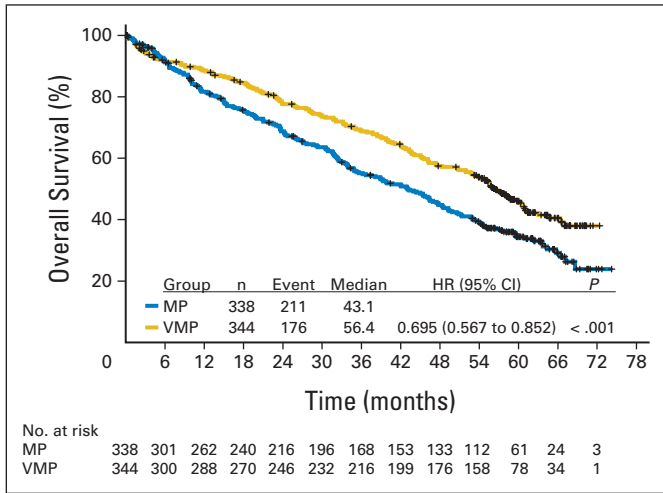
RESULTS

Patients

Baseline characteristics have been reported[11] and were well balanced between treatment arms. Overall, median age was 71 years, 30% of patients were age ≥ 75 years, and 34% had ISS stage III MM. At data cutoff, only 16 patients (5%) in each arm had been lost to follow-up (Fig 1).

OS

After a median follow-up of 5 years (60.1 months; range, 0 to 74 months) from random assignment, 176 patients (51%) randomly assigned to VMP and 211 (62%) randomly assigned to MP had died (Fig 1). There was a 31% reduced risk of death following VMP versus MP (HR, 0.695; $P < .001$; Fig 2). Median OS was 56.4 versus 43.1 months; 5-year OS rates were 46.0% (95% CI, 40.3% to 51.8%) and 34.4% (95% CI, 28.9% to 39.9%), respectively.

The OS benefit with VMP was seen across prespecified patient subgroups, including those age ≥ 75 years (median, 50.7 v 32.9 months; HR, 0.70), those younger than 75 years (median, 58.6 v 47.7 months; HR, 0.69), patients with ISS stage III MM (median, 46.2 v 30.5 months; HR, 0.63), and those with creatinine clearance less than 60 mL/min (median, 56.8 v 36.7 months; HR, 0.70; Fig 3). However, no significant difference was observed in the small subgroup with documented high-risk cytogenetics (n = 46; Fig 3); because of low patient numbers, additional analyses by individual cytogenetic abnormalities were not feasible.

Fig 1. Updated CONSORT diagram showing patient flow through the study. PD, progressive disease; SPM, second primary malignancy.

Multivariate Cox regression analysis of OS according to best response demonstrated a clear impact of response on improved outcome. OS was significantly improved with complete response versus less-than-complete response by intent-to-treat analysis (HR, 0.675; 95% CI, 0.486 to 0.936; $P = .0184$; VMP arm: HR, 0.708; 95% CI, 0.484 to 1.036; $P = .0755$; MP arm: HR, 0.710; 95% CI, 0.303 to 1.662; $P = .4301$). There was also a trend toward improved OS with complete versus partial response by intent-to-treat analysis (HR, 0.761; 95% CI, 0.540 to 1.071; $P = .1173$).

Subsequent Therapies and TTNT

In all, 215 (63%) of 344 VMP and 246 (73%) of 338 MP patients had received subsequent anti-MM therapies. Use of subsequent tha-lidomide or lenalidomide was similar between arms, with 103 (30%) of 344 VMP patients and 122 (36%) of 338 MP patients having received subsequent thalidomide and 84 (24%) and 63 (19%) subsequent lenalidomide (Appendix Table A1, online only). A lower proportion of VMP versus MP patients received subsequent bortezomib (22% [n = 77] versus 43% [n = 145]); this imbalance was also seen in the small subgroup of patients with high-risk cytogenetics (Appendix Table A1). Investigator-assessed response rates to subsequent bort-ezomib and/or bortezomib-containing regimens were 50% following VMP (ie, bortezomib re-treatment) and 58% following MP, were 46% and 55%, respectively, to subsequent thalidomide and/or thalido-mide-containing regimens, and were 62% and 56%, respectively, to subsequent lenalidomide and/or lenalidomide-containing regimens.

Fig 2. Overall survival (intent-to-treat analysis) in patients randomly assigned to bortezomib-melphalan-prednisone (VMP) or melphalan-prednisone (MP) after a median follow-up of 5 years. HR, hazard ratio.
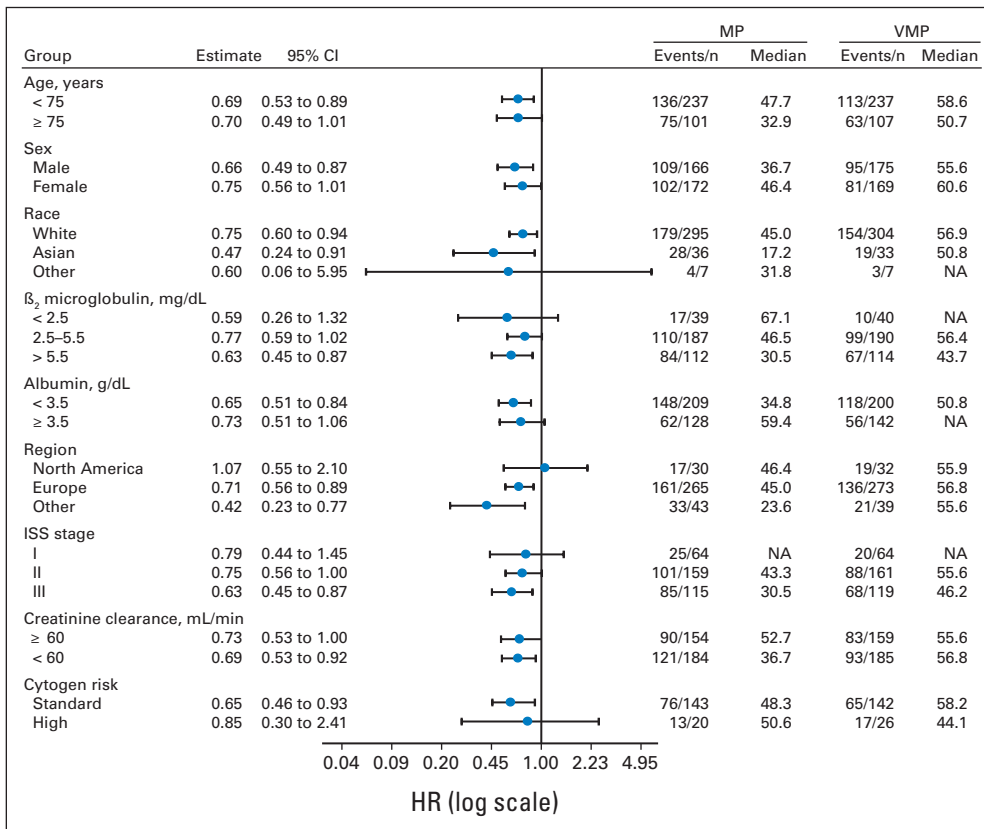
Use of older agents was generally similar between arms (Appendix Table A1). TTNT (median, 30.7 v 20.5 months; HR, 0.557; $P < .001$) and TFI (median, 19.4 v 9.1 months; HR, 0.573; $P < .001$) were longer with VMP versus MP by cumulative incidence analysis (Table 1).

To assess whether VMP induced more resistant relapses, we compared survival from start of subsequent therapy and showed that it was similar between arms (HR, 0.914; 95% CI, 0.719 to 1.163; Fig 4). Moreover, to investigate the treatment paradigm of first-line MP

followed by subsequent salvage bortezomib, we compared OS in all VMP patients with OS in MP patients who had received salvage therapy with bortezomib (n = 145), not yet relapsed (n = 78), or died without receiving subsequent therapy (n = 14). Median OS was 56.4 versus 45.4 months, respectively (HR, 0.714; 95% CI, 0.571 to 0.892; $P = .0029$). Similar results were observed in an analysis incorporating MP patients who received bortezomib at first relapse only (HR, 0.638; 95% CI, 0.499 to 0.817; $P < .001$).

Second Primary Malignancies

In all, 327 VMP patients (95%) and 328 MP patients (97%) were included in the analyses of second primary malignancies (Table 2). Incidence proportions of all malignancies and of fatal hematologic malignancies and solid tumors were similar between arms (Table 2). Nineteen (6%) of 327 patients in the VMP arm and 13 (4%) of 328 patients in the MP arm reported second primary malignancies. Three patients (1%) in each arm had hematologic malignancies: two patients in each arm had acute myeloid leukemia (fatal in all four patients), one patient in the MP arm had B-cell non-Hodgkin lymphoma that was fatal, and one patient in the VMP arm had myelodysplastic syndrome. In the VMP arm, these hematologic malignancies were reported at 18, 47.4, and 48 months after the start of treatment; in the MP arm, the malignancies occurred at 1, 8.8, and 35 months. Sixteen patients (5%) in the VMP arm and 10 patients (3%) in the MP arm had second primary nonhematologic malignancies that were mostly gastrointestinal (five, VMP; four, MP) and renal or prostate (four, VMP; three, MP) tumors. These were fatal in six patients (2%) in each arm. These malignancies occurred after a median of 22.7 months (range, 1 to 56

Group	Estimate	95% CI		MP Events/n	MP Median	VMP Events/n	VMP Median
Age, years							
< 75	0.69	0.53 to 0.89		136/237	47.7	113/237	58.6
≥ 75	0.70	0.49 to 1.01		75/101	32.9	63/107	50.7
Sex							
Male	0.66	0.49 to 0.87		109/166	36.7	95/175	55.6
Female	0.75	0.56 to 1.01		102/172	46.4	81/169	60.6
Race							
White	0.75	0.60 to 0.94		179/295	45.0	154/304	56.9
Asian	0.47	0.24 to 0.91		28/36	17.2	19/33	50.8
Other	0.60	0.06 to 5.95		4/7	31.8	3/7	NA
ß$_2$ microglobulin, mg/dL							
< 2.5	0.59	0.26 to 1.32		17/39	67.1	10/40	NA
2.5–5.5	0.77	0.59 to 1.02		110/187	46.5	99/190	56.4
> 5.5	0.63	0.45 to 0.87		84/112	30.5	67/114	43.7
Albumin, g/dL							
< 3.5	0.65	0.51 to 0.84		148/209	34.8	118/200	50.8
≥ 3.5	0.73	0.51 to 1.06		62/128	59.4	56/142	NA
Region							
North America	1.07	0.55 to 2.10		17/30	46.4	19/32	55.9
Europe	0.71	0.56 to 0.89		161/265	45.0	136/273	56.8
Other	0.42	0.23 to 0.77		33/43	23.6	21/39	55.6
ISS stage							
I	0.79	0.44 to 1.45		25/64	NA	20/64	NA
II	0.75	0.56 to 1.00		101/159	43.3	88/161	55.6
III	0.63	0.45 to 0.87		85/115	30.5	68/119	46.2
Creatinine clearance, mL/min							
≥ 60	0.73	0.53 to 1.00		90/154	52.7	83/159	55.6
< 60	0.69	0.53 to 0.92		121/184	36.7	93/185	56.8
Cytogen risk							
Standard	0.65	0.46 to 0.93		76/143	48.3	65/142	58.2
High	0.85	0.30 to 2.41		13/20	50.6	17/26	44.1

HR (log scale): 0.04 0.09 0.20 0.45 1.00 2.23 4.95

Fig 3. Subgroup analyses of overall survival. *P* values for subgroup interaction tests were all nonsignificant (range, .1394 [region: other] to .9352 [age: ≥ 75 years]). HR, hazard ratio; ISS, International Staging System; MP, melphalan-prednisone; NA, not assessable; VMP, bortezomib-melphalan-prednisone.

Table 1. TTNT in Patients Randomly Assigned to VMP or MP and TFI in the Treated Population, Analyzed by Cumulative Incidence Using the Competing Risk Approach

	TTNT								TFI							
	VMP (n = 344)					MP (n = 338)			VMP (n = 340)					MP (n = 337)		
Variable	No.	%	HR*	95% CI	P†	No.	%	95% CI	No.	%	HR*	95% CI	P†	No.	%	95% CI
Events	224	65				260	77		224	66				260	77	
Censored/competing events	120	35				78	23		116	34				77	23	
TTNT/TFI, months																
25% quartile‡	17.1					10.0			7.1					2.2		
50% quartile‡	30.7					20.5			19.4					9.1		
75% quartile‡	N/E					34.8			52.7					24.1		
Event-free survival rate‡			0.557	0.462 to 0.671	< .001						0.573	0.476 to 0.690	< .001			
1 year		85.1		81.1 to 88.7			71.3	66.3 to 76.1		62.0		56.8 to 67.3			44.1	38.9 to 49.7
2 year		60.5		55.3 to 65.8			40.9	35.7 to 46.5		46.3		41.1 to 51.9			25.1	20.7 to 30.3
3 year		45.2		40.0 to 50.8			24.4	20.0 to 29.5		36.1		31.1 to 41.6			19.4	15.5 to 24.2
4 year		35.7		30.7 to 41.2			19.6	15.6 to 24.5		30.9		26.0 to 36.5			18.1	14.2 to 22.9
5 year		31.5		26.6 to 37.0			18.3	14.4 to 23.2		25.9		20.4 to 32.4			15.6	10.5 to 22.9

Abbreviations: HR, hazard ratio; MP, melphalan-prednisone; N/E, not estimable; TFI, treatment-free interval; TTNT, time to next therapy; VMP, bortezomib-melphalan-prednisone.
*Based on the cause-specific hazard.
†Based on a stratified log-rank test comparing cause-specific hazards for subsequent treatment.
‡Based on cumulative incidence estimates.

months) in the VMP arm and 30.3 months (range, 3 to 63 months) in the MP arm.

The overall observation or exposure period for recording occurrence of second primary malignancies was asymmetric, being longer in the VMP arm compared with the MP arm because more patients remained alive for a longer period on that arm. Exposure in the VMP arm was greater than in the MP arm by 163 patient-years (1,167 *v* 1,004 patient-years, respectively; Table 2). The exposure-adjusted incidence rates for all second primary malignancies, which take into account this longer observation period, were similar between arms (0.0166 and 0.013 per patient-year for VMP and MP, respectively).
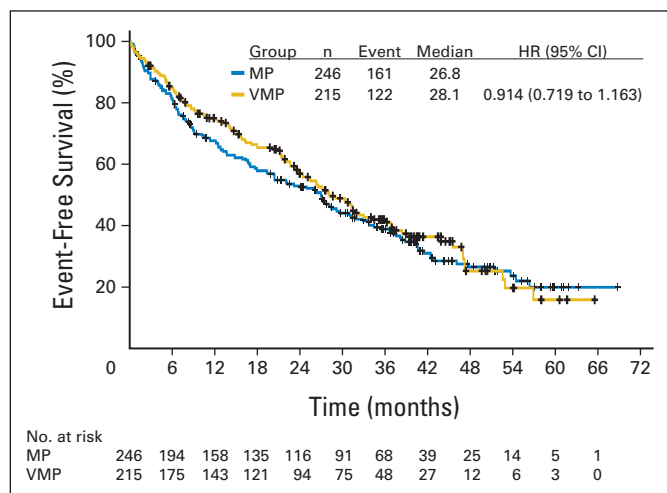
Fig 4. Analysis of survival from start of subsequent therapy in all randomly assigned patients who received subsequent therapy. HR, hazard ratio; MP, melphalan-prednisone; VMP, bortezomib-melphalan-prednisone.

DISCUSSION

The findings of this final analysis of the VISTA phase III trial demonstrate a persistent significant OS benefit with VMP versus MP. These data are highly robust because of the large patient population and lengthy follow-up and show that VMP resulted in a substantial long-term OS benefit versus MP, with a 13.3-month increase in the median. This benefit compares favorably with the 6.6-month increase in median OS (39.3 *v* 32.7 months) reported in a meta-analysis of six phase III trials of MP plus thalidomide (MPT) versus MP.[19] The HR for OS in this meta-analysis was 0.83 (95% CI, 0.73 to 0.94; *P* = .004), representing a 17% reduced risk of death with MPT[19] compared with the 31% reduced risk of death with VMP versus MP reported here. Notably, the median follow-up in seven individual studies of MPT versus MP ranges from 23 to 51.5 months,[12-18] compared with the 60.1-month follow-up for the analysis reported here. In addition, it should be noted that the OS benefit observed in this trial was not due to a poor outcome with MP, since median OS with MP in this trial (43.1 months) was longer than median OS with MP in the MPT trial meta-analysis (32.7 months). The median OS observed with VMP (56.4 months) appears similar to that previously reported after long-term follow-up from studies of high-dose therapy and autologous stem-cell transplantation conducted in the 1990s and early 2000s (median, 4.0 to 5.7 years)[37]; however, as reviewed recently, it should be noted that results from transplantation studies have also significantly improved in the past decade with the combination of novel drugs (median of approximately 7 to 10 years).[37]

Importantly, the OS benefit with VMP versus MP was seen across multiple prespecified patient subgroups, including similar benefit in elderly (age ≥ 75 years) and younger patients, and the HR in favor of VMP was generally consistent with that for the overall population,

Table 2. Incidence Proportion and Exposure-Adjusted Incidence Rate in Patient-Years of Second Primary Malignancies Following Treatment With VMP and MP

Second Primary Malignancy	VMP		MP		RR*	95% CI
	No.	%	No.	%		
Patients with data collected	327		328			
Hematologic	3	1	3	1	1.003	0.204 to 4.933
Acute myeloid leukemia	2	1	2	1		
B-cell lymphoma	0		1	< 1		
Myelodysplastic syndromes	1†	< 1	0			
Fatal hematologic	2	1	3	1	0.669	0.113 to 3.976
Nonhematologic	16	5	10	3	1.605	0.739 to 3.484
GI	5†	2	4	1		
Renal/prostate	4†	1	3†	1		
Respiratory	2†	1	0			
Skin	2†	1	0			
Other	3†	1	3†	1		
Fatal nonhematologic	6	2	6	2	1.003	0.327 to 3.078
Patient-years for which data collected	1,167		1,004			
Hematologic per patient-year‡	0.0026		0.0030		0.862	0.174 to 4.269
Fatal	0.0017		0.0030		0.574	0.096 to 3.436
Nonhematologic per patient-year‡	0.0140		0.0100		1.389	0.630 to 3.061
Fatal	0.0052		0.0060		0.859	0.277 to 2.664
Overall per patient-year‡	0.0166		0.0130			

Abbreviations: MP, melphalan-prednisone; RR, relative risk; VMP, bortezomib-melphalan-prednisone.
*RR < 1 favors VMP.
†Nonfatal malignancies, including one myelodysplastic syndrome on VMP arm, three GI on VMP arm, two renal/prostate on each arm, one respiratory on VMP arm, two skin on VMP arm, and two "other" on each arm.
‡Incidence rate.

indicating the applicability of these findings to the broad MM population. However, there was an absence of OS benefit among the small subgroup of patients with documented high-risk cytogenetics (Fig 3), whereas bortezomib-based therapy has previously been shown to result in high response rates and promising long-term outcomes in such patients.[10,11,38-47] The limited sample size prevents any meaningful conclusions from being drawn.

As reported for the previous analysis of VISTA,[10] VMP continued to provide a significant clinical benefit versus MP in terms of prolonged TTNT and TFI. TTP and PFS could not be updated at this final analysis because they were based on central laboratory assessment and, because of the highly significant initial benefit observed for these end points,[11] it was decided to stop central assessment following the initial analysis.

Survival from the start of subsequent therapy was similar between arms, indicating that VMP did not induce more resistant relapses. This finding is particularly notable because this analysis contained a bias in favor of MP-treated patients, because it excluded a higher proportion of VMP-treated patients who experienced most benefit (ie, those who had not yet required subsequent therapy and were thus most sensitive to therapy or had better prognosis). In addition, OS with VMP was significantly longer versus the treatment paradigm of first-line MP followed by salvage bortezomib (ie, MP patients who did receive, or could have received, bortezomib at relapse). Overall, these findings demonstrate the importance of a treatment paradigm of providing optimal first-line treatment, rather than reserving novel agents for salvage therapy.

To the best of our knowledge, this is the first paper reporting the incidence of second primary malignancies with bortezomib-based treatment. It is important to highlight that less than 5% of patients were lost to follow-up. With this thorough data collection, we identified no increased risk of second primary malignancies with VMP versus MP. Importantly, overall incidence rates in both arms (VMP, 0.017 and MP, 0.0130 per patient-year) were consistent with the background incidence rate of 0.019 for all cancers in the general US population age 65 to 74 years, as reported for 2004 to 2008 by the SEER Program.[48] These data indicate that use of bortezomib for up to approximately 1 year does not add to the previously reported leukemogenic effect of melphalan,[24,27,29] with the incidence rates of secondary hematologic malignancies low and similar in both the VMP and MP arms. Addition of lenalidomide to MP and use of maintenance lenalidomide until progression (median PFS, 31 months) has been suggested to result in a small increased risk of secondary leukemia compared with MP alone, although this may be associated with the presence of complex cytogenetics at baseline.[20] However, the increased risk of secondary malignancies with lenalidomide maintenance, which has also been shown post-transplantation,[28,31] is counterbalanced by the highly significant PFS benefit demonstrated,[20,28,31] together with an OS benefit in one study.[31] Moreover, incidence rates were low, with no increase seen, in another study of lenalidomide-based therapy in the first-line setting.[34]

In conclusion, initial treatment of patients with MM who are ineligible for transplantation with VMP results in a significant reduction in the risk of death compared with initial treatment with MP that is maintained after 5 years of follow-up and despite substantial use of salvage therapies based on novel agents. Furthermore, our exploratory analysis identified no emerging safety signal for second primary malignancies following treatment with VMP.

AUTHOR CONTRIBUTIONS

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