Morabito F, Bringhen S, Larocca A, Wijermans P, Victoria Mateos M, Gimsing P, Mazzone C, Gottardi D, Omede P, Zweegman S, Jose Lahuerta J, Zambello R, Musto P, Magarotto V, Schaafsma M, Oriol A, Juliusson G, Cerrato C, Catalano L, Gentile M, Isabel Turel A, Marina Liberati A, Cavalli M, Rossi D, Passera R, Rosso S, Beksac M, Cavo M, Waage A, San Miguel J, Boccadoro M, Sonneveld P, Palumbo A, Offidani M.
Bortezomib, melphalan, prednisone (VMP) versus melphalan, prednisone, thalidomide (MPT) in elderly newly diagnosed multiple myeloma patients: A retrospective case-matched study.
AMERICAN JOURNAL OF HEMATOLOGY (2014)

Bortezomib, melphalan, prednisone (VMP) versus melphalan, prednisone, thalidomide (MPT) in elderly newly diagnosed multiple myeloma patients: A retrospective case-matched study

Fortunato Morabito,[1]* Sara Bringhen,[2] Alessandra Larocca,[2] Pierre Wijermans,[3] Maria Victoria Mateos,[4] Peter Gimsing,[5] Carla Mazzone,[1] Daniela Gottardi,[6] Paola Omede`,[2] Sonja Zweegman,[7] Juan Jos_e Lahuerta,[8] Renato Zambello,[9] Pellegrino Musto,[10] Valeria Magarotto,[2] Martijn Schaafsma,[11] Albert Oriol,[12] Gunnar Juliusson,[13] Chiara Cerrato,[2] Lucio Catalano,[14] Massimo Gentile,[1] Ana Isabel Turel,[15] Anna Marina Liberati,[16] Maide Cavalli,[17] Davide Rossi,[18] Roberto Passera,[19] Stefano Rosso,[20] Meral Beksac,[21] Michele Cavo,[22] Anders Waage,[23] Jesus San Miguel,[24] Mario Boccadoro,[2] Pieter Sonneveld,[25] Antonio Palumbo,[2] and Massimo Offidani[26]

[1]UOC Ematologia, A.O. di Cosenza, Torino, Italy; [2]Myeloma Unit, Division of Hematology, AOU S. Giovanni Battista, Torino, Italy; [3]Department of Hematology, Haga Hospital, the Hague, The Netherlands; [4]Hematology Department, University Hospital of Salamanca, Salamanca, Spain; [5]Department of Hematology, Rigs hospitalet and University of Copenhagen, Denmark; [6]SCDU Ematologia e Terapie Cellulari, A.O. Ordine Mauriziano – Umberto I, Torino, Italy; [7]Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands; [8]Hematology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; [9]Padova University School of Medicine, Department of Clinical and Experimental Medicine, Hematology and Clinical Immunology, Padova, Italy; [10]Department of Onco-Haematology, IRCCS, Referral Cancer Centre of Basilicata, Rionero in Vulture (Pz), Italy; [11]Medical Spectrum Twente, Enschede, The Netherlands; [12]Clinical Hematology, Institut Catal_a d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [13]Department of Hematology, Stem Cell Center, Lund University, and Skåne University Hospital, Lund, Sweden;[14]Divisione di Ematologia, Universit_a Federico II, Napoli, Italy; [15]Hematology and Oncology Service, Hospital Cl_ınico Universitario, Valencia, Spain; [16]Department of Transplant Oncohematology, Perugia University, S. Maria, Terni, Italy; [17]Divisione di Ematologia, Ospedale Ferrarotto, Universt_a di Catania, Catania, Italy; [18]Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; [19]Divisione di Medicina Nucleare 2 AO Città della Salute e della Scienza di Torino, Italy; [20]Registro Tumori Regione Piemonte AO Citt_a della Salute e della Scienza di Torino, Italy; [21]Department of Hematology, Faculty of Medicine, Ankara University, Ankara, Turkey; [22]Ser_agnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [23]Department of Hematology, St Olavs Hospital/NTNU, Trondheim, Norway; [24]Servicio de Hematolog_ıa, Hospital Universitario de Salamanca, CIC, IBMCC (USAL-CSIC), Spain; [25]Erasmus Medical Center, Rotterdam, The Netherlands; [26]Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona, Ancona, Italy

Abstract

Novel agents in combination with melphalan and prednisone (MP) significantly improved progression-free survival (PFS) and overall survival (OS) in multiple myeloma (MM). Randomized trials comparing MP plus bortezomib (VMP) versus MP plus thalidomide (MPT) are lacking. Nine hundred and fifty-six elderly (>65 years) newly diagnosed MM patients from six European randomized trials were retrospectively analyzed and matched for age, albumin, and beta2-microglobulin at diagnosis, 296 patients were selected from the VMP groups, and 294 from MPT. Complete response rate was 21% in the VMP patients and 13% in the MPT patients (P = 0.007). After a median follow-up of 34 months (range, 1–92), VMP significantly prolonged both PFS (median 32.5 vs. 22.9 months, HR 0.65; 95% CI 0.52–0.82; P < 0.001) and OS (median 79.7 vs. 45.1 months, HR 0.44; 95% CI 0.32–0.59; P < 0.001) in comparison with MPT. The benefit in terms of OS of the VMP group was quite similar among patients with different risk factors defined by sex, ISS, ECOG performance status, or serum creatinine but not among patients ≥75 years. Multivariate analysis confirmed that VMP was an independent predictor of longer PFS and OS. In a control-case matched analysis, PFS and OS were prolonged in patients who received VMP in comparison with those treated with MPT. Am. J. Hematol. 89:355–362, 2014. © 2013 Wiley Periodicals, Inc.

Introduction

A meta-analysis of 27 randomized trials showed that melphalan plus prednisone (MP) was as effective as several combination chemotherapies in prolonging overall survival (OS) [1]. In elderly multiple myeloma (MM) patients, MP has been the reference treatment for several decades.

Meta-analysis [2, 3] of data from six randomized trials [4-9] showed that combination of thalidomide and MP (MPT) improved progression-free survival (PFS) and OS compared with MP alone in transplant ineligible MM patients. Only two [5, 6] of the six [4-9] phase III trials comparing MPT vs. MP demonstrated OS benefit. Overall, MPT regimen led to 17% risk reduction of death compared with MP and increased median OS by 6.6 months [3].

The clinical relevance of the combination bortezomib plus MP (VMP) has been explored in large randomized trials [10-15]. In the VISTA trial, VMP was superior to MP, with risk reductions in progression (52%) and in death (31%) [10-12]. In two subsequent studies, a reduced intensity schedule (once-weekly) of bortezomib significantly decreased the incidence of peripheral neuropathy without any negative effect on PFS or OS [14, 15]. In elderly patients, first-line therapy including novel agents enhanced survival, although to a lesser degree [16] mainly due to treatment-related toxicities. Thus, the concomitant presence of multiple diseases in these patients greatly influences treatment decisions and requires judicious screening and necessary support [16].

MPT and VMP regimens are now regarded the new standard of care for untreated MM patients ≥65 years. No randomized trial comparing MPT vs. VMP has been performed. In this case-matched study of individual patient data (matched for age, albumin and beta2-microglobulin) from six randomized trials, we assessed the impact of treatment on outcome in elderly untreated MM patients receiving MPT or VMP.

Methods

Patient selection

Patients with untreated MM, ineligible for autologous transplantation, enrolled in the VMP or MPT arms of six published European phase III trials—GISMM-2001, HOVON49, NMSG, PETHEMA-GEM05MAS65, GIMEMA-MM0305, and TMSG—were evaluated [4, 7-9, 13, 14]. We evaluated only patients >65 years since the studies had different eligible age ranges. We analyzed data only from European groups who wished to participate in the study. Data of IFM 99-06, IFM 01/01, and VISTA trials were not available for this analysis. Details on treatment regimens (Table 1) and results have previously been reported [4, 7-9, 13, 14]. To increase comparability among treatment arms, we matched patients in homogenous strata defined by k-means clustering [17] that assigned each observation to the nearest mean in the data space here consisting of three variables considered influential on main outcomes: age, albumin, and beta2-microglobulin at diagnosis, treated as continuous variables. The K-means method identified and then clustered those patients with the nearest average distance in the metric of a set of predefined variables. Thus, from an overall source population of 956 patients, 590 patients in either MTP or VMP arms were selected retrospectively.

Table 1. Description of the Trials

Trial	Country	No. of pts	Inclusion year	Age, y	SD stage	WHO status	Schedule	No. of cycles/ interval (weeks)	Maintenance
GISMM-2001[4]	Italy	331	2002-05	> 65	II, III	0–4	M: 4 mg/m2 days 1–4; P: 40 mg/m2 days 1–7; ± Thal: 100 mg/day	6/4	Thal: 100 mg until relapse for pts treated with MPT
HOVON49[8]	The Netherlands/ Belgium	333	2002-07	> 65	Ib, II, III	0–3	M: 0.25 mg/kg days 1–5; P: 1 mg/kg days 1–5; ± Thal: 200 mg/day	8/4	Thal: 50 mg until relapse for pts treated with MPT
NMSG12[7]	Nordic	357	2002-07	> 65	I-III symptomatic	0–4	M: 0.25 mg/kg days 1–4; P: 100 mg days 1–4; ± Thal: 200–400 mg/day	Until plateau/6	Thal: 200 mg/day from plateau until relapse for pts treated with MPT
TMSG[9]	Turkey	114	2006-09	> 55	I-III symptomatic	0–2	M: 9 mg/m2 days 1–4; P: 60 mg/m2 days 1–7; ± Thal: 100 mg/day	8/6	No
GIMEMA-0305[13]	Italy	511	2006-09	> 65	I-III symptomatic	0–2	M: 9mg/m2 days 1–4; P: 60mg/m2 days 1–4; Vel: 1.3 mg/m2 days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1–4 and on days 1, 8, 22, and 29 during cycles 5–9; ± Thal: 50 mg/day[a]	9/6[a]	Vel: 1.3 mg/m2 every 14 days + Thal: 50 mg/ day for 2 years or until progression or relapse for pts treated with VMPT
PETHEMA-GEM05MAS65[14]	Spain	260	2006-08	> 65	I-III symptomatic	0–2	Vel: 1.3 mg/m2 days 1, 4, 8, 11, 22, 25, 29, and 32 during cycle 1 and on days 1, 8, 22, and 29 during cycles 2–6; M: 9mg/m2 days 1–4; P: 60mg/m2 days 1–4; vs. Vel: 1.3 mg/ m2 days 1, 4, 8, 11, 22, 25, 29, and 32 during cycle 1 and on days 1, 8, 22, and 29 during cycles 2–6 P: 60 mg/m2 days 1–4; Thal: 100 mg/day	6/6 (5 for cycle 1)	Patients completed the 6 cycles were randomly assigned to maintenance schedule: Vel: 1.3 mg/m2 days 1, 4, 8, 11 every 3 months P: 50 mg every 48 h or Vel: 1.3 mg/m2 days 1, 4, 8, 11 every 3 months Thal: 50 mg daily for up to 3 years or until progression or relapse

M: melphalan; P: prednisone; Thal: thalidomide; Vel: bortezomib.

[a] After the inclusion of the first 139 patients, both VMPT and VMP induction schedules were changed to nine 5-week cycles and Vel was administered on days 1, 8, 15, and 22 during cycles 1 to 9.

Overall, 296 patients were selected from the VMP groups, 180 and 116 from GIMEMA-MM0305 [13] and PETHEMA-GEM05MAS65 trials [14], respectively. Moreover, 125/296 cases received bortezomib once-weekly, 38 received twice-weekly, and 133 received twice-weekly for the first few cycles (range 1–4 cycles) and subsequently once-weekly. A further 294 cases were chosen from the MPT arms, 80 from HOVON-49 [8], 89 from GISMM-2001 [4], 96 from NMSG [7], and 29 from TMSG trial [9]. Patients were treated between 2002 and 2009 with median follow-up of 34 months (range 1–92) for the whole cohort, 34 (1–81) for the MPT group, and 34 (1–92) for VMP. Primary and secondary endpoints were OS and PFS, respectively, according to International Myeloma Working Group (IMWG) criteria. Selection bias was investigated comparing survival between selected and discarded cases in the two study arms: no differences were detected for the VMP group, while there was a slightly worse survival of the discarded cases among the MPT group (data not shown). Therefore, the comparison of the VMP group was against the better-performing selection of cases from the MPT group, with a possible underestimation of the net effect and with no inflation of the results.

The institutional review board at each participating center approved trials that were performed in accordance with the Declaration of Helsinki. All patients provided written informed consent. Trials were registered at ClinicalTrials.gov or controlled-trials.com: NCT00232934 [4], NCT00218855 [7], ISRCTN90692740 [8], NCT01063179 [13], NCT00443235 [14], and NCT00934154 [9]. This retrospective study was approved by each single institutional review board responsible for the original prospective trial.

Assessment

Data were collected at each coordinating center, sent to a central coordinating center, reviewed for consistency and completeness, and entered into a new database. Age, gender, creatinine value, Durie-Salmon stage, ISS score, ECOG Performance Status (PS), serum calcium, and Ig isotype together with date of progression or date of last follow-up, date of death or of last follow-up, best response achievement, and grade of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events, v3.0 were collected. In HOVON-49 and GEM05MAS65 trials, responses were initially determined using the European Group for Blood and Marrow Transplantation criteria [18] and re-evaluated using IMWG criteria [19]. For GISMM-2001, NMSG, TMSG, and GIMEMA-MM0305 trials, responses were assessed using IMWG criteria [19]. The relapse criteria utilized are reported in Supporting Information Table 1.

Statistical analysis

OS was defined as the time from study entry to death due to any cause, and PFS as the time from study entry until progression or death due to myeloma; in both cases, patients still alive were censored at the date of last contact.

Kaplan-Meier curves for PFS and OS were calculated for the chemotherapy regimens (VMP vs. MPT) [20]. Variables influencing OS and PFS were initially screened with Cox univariate analysis. Independent effects of possible determinants were then analyzed in multivariate Cox proportional hazards models [21] stratified on the k-means clusters. Cox univariate analysis was performed for the following prognostic factors: chemotherapy regimen (VMP vs. MPT), age at diagnosis ($\geq$75 vs. <75 yrs), gender, Durie-Salmon stage, ISS score, PS ($\geq$2 vs. 0–1), serum creatinine (>1.2 vs. $\leq$1.2 mg/dl), serum calcium (>2.35 vs. $\leq$2.35 mg/dl), Ig isotype, and best response achievement (CR/VGPR/PR vs. <PR). Best response achievement was treated as a time-dependent variable, including in the Cox models an interaction term built as product of the dichotomous dummy variable for treatment and the observed follow-up time at the event.

Patient characteristics were tested using the Pearson $\chi 2$ test for categorical variables and the Mann-Whitney test for continuous ones. All reported P-values were two-sided, at the conventional 5% significance level. Data were analyzed as of December 2012 using IBM SPSS (v20.0.0, IBM Corporation, New York) and R v2.15.1 (The R Foundation for Statistical Computing, Vienna).

Results

Starting with 956 cases, we first eliminated cases lacking beta2-microglobulin and albumin data, and the remaining 817 cases were complete for age and beta2-microglobulin and albumin. Out of 817 cases, 590 were selected by k-means clustering. Baseline characteristics were well balanced between the two groups, although a higher percentage of worse PS cases were present in the VMP group (Table 2). Median age was 72 years (IQR, 69–76 years); about 30% of patients were ≥75 years in both groups.

Table 2. Baseline Characteristics of Patients

	VMP ($n = 296$)		MPT ($n = 294$)		
Variable	n	%	n	%	p
Age, years					
Median	72		72		
IQR	69–76		69–76		
≥75	115	30	115	30	0.9
Male, sex	147	50	165	56	0.1
Isotype					
IgG	184	62	200	68	
IgA	76	26	70	24	0.039
Light chain	34	11	17	6	
Data missing	2	1	7	2	
ECOG Performance status					
0–1	83	28	189	64	
2–4	96	32	89	30	<0.0001
Data missing	117	40	16	6	
International Staging System stage					
I	90	30	72	25	
II	129	44	159	54	0.038
III	77	26	63	21	
Data missing	0		0		
Creatinine					
Median	1.00		0.97		
≥1.2 mg/dl	81	27	91	31	0.33
Data missing	0		0		
Albumin					
Median	3.7		3.6		
≤3.5 mg/dl	119	40	126	43	0.51
Data missing	0		0		
β2-microglobulin					
Median	3.7		3.8		
≥3.5 mg/L	125	42	131	45	0.49
Data missing	0		0		

IQR, interquartile range; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group; VMP, bortezomib-melphalan-prednisone; MPT, melphalan-prednisone-thalidomide.

Response rate

A greater proportion of patients in the VMP group had a CR, VGPR, or PR after induction therapy (Table 3). The CR rate was 21% in the VMP group and 13% in the MPT (P = 0.007), the ≥PR rate was 78% in the VMP group and 69% in the MPT (P = 0.01).

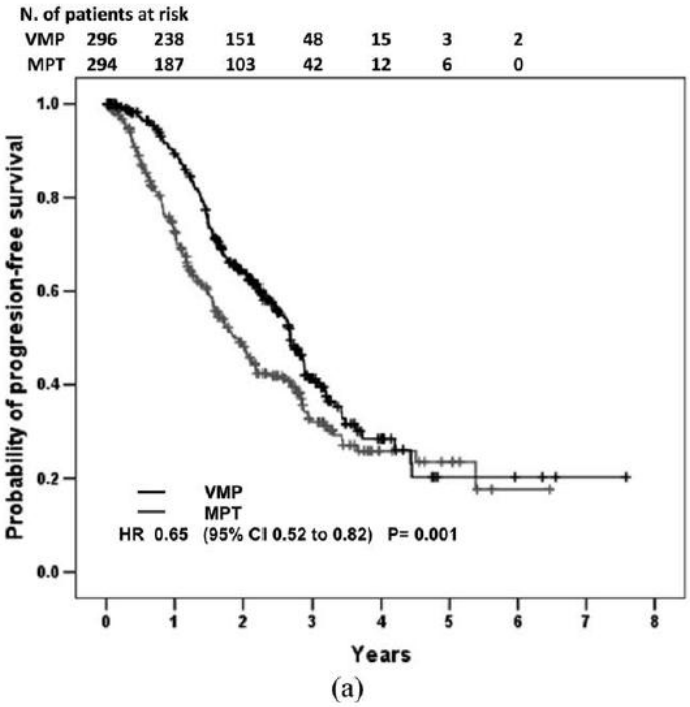
Table 3. Response Rate

Response	VMP (*n* = 296) *n* (%)	MPT (*n* = 294) *n* (%)	*P* value
Best response according to International Uniform Response Criteria			
Complete, very good partial or partial response	231 (78)	202 (69)	0.01
Complete response	62 (21)	37 (13)	0.007
Very good partial response	58 (20)	54 (18)	0.7
Partial response	111 (37)	111 (37)	0.95
Stable disease	58 (20)	70 (24)	0.214
Progressive disease	2 (1)	5 (2)	0.25
Not available	5 (2)	17 (6)	0.009

VMP, bortezomib-melphalan-prednisone; MPT, melphalan-prednisone-thalidomide.

Progression-free survival

After a median follow-up of 34 months (range, 1–92), 318 patients (54%) relapsed or died. For the entire population, median PFS was 29 months (IQR, 14.8–53.9); median PFS was 32.5 months in the VMP group, and 22.9 months for MPT patients (P = 0.001). The three-year PFS rate was 41.3% in VMP cases and 32.8% in MPT cases (Fig. 1, Panel A). VMP led to 35% reduced risk of progression or death compared with MPT. A statistically significant PFS benefit with VMP was observed in patients <75 years, in females, in all subgroups of patients defined by Durie-Salmon, ISS stage III, creatinine <1.2 mg/dL, IgA isotype and in cases achieving PR (Fig. 2). A multivariate model showed that for VMP achievement of a better response and PS at baseline were independent predictors of prolonged PFS (Table 4). When patients were stratified by trial, cases treated with VMP in PETHEMA-GEM05MAS65 showed a statistically better PFS than cases treated with MPT in NMSG, HOVON-49, and TMSG trials but were not different than cases treated with MPT in GISMM-2001, while cases treated with VMP in GIMEMA-MM0305 showed a statistically better PFS than cases treated with MPT in HOVON-49 trial, were not different than cases treated with MPT in NMSG and TMSG trials, and were worse than cases treated with MPT in GISMM-2001 (Supporting Information Figure 1, Panel A).



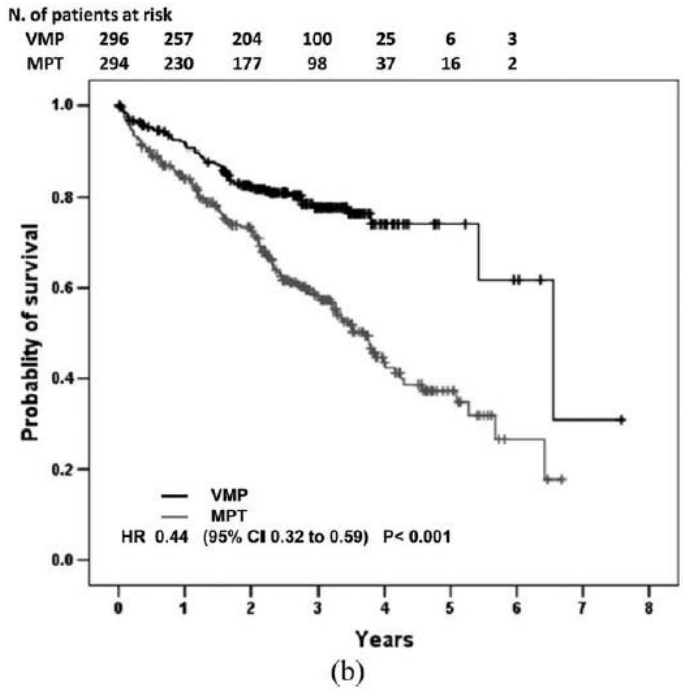


Figure 1. Kaplan–Meier curves for progression-free survival and overall survival in the intention-to-treat population. Panel A shows progression-free survival; the median progression free survival was 32.5 months in the VMP group and 22.9 months in the MPT patients (P = 0.001). The three-year progression-free survival rate was 41.3% in subjects treated with VMP and 32.8% in those treated with MPT. Panel B shows overall survival; the median overall survival was 79.7 months in the VMP group and 45.1 months in the MPT group (P < 0.001). The three-year overall survival rate was 77.8% in subjects treated with VMP and 58.5% in those treated with MPT.

Variable	HR	95%CI	P
age<75	0.71	0.55-0.92	0.009
age>75	0.68	0.44-1.03	0.071
male	0.75	0.55-1.02	0.065
female	0.66	0.48-0.91	0.011
DS I+II	0.53	0.36-0.79	0.002
DS III	0.67	0.48-0.93	0.017
ISS I	0.73	0.47-1.12	0.149
ISS II	0.81	0.59-1.10	0.168
ISS III	0.53	0.33-0.86	0.009
creat < 1.2	0.68	0.53-0.88	0.003
creat > 1.2	0.77	0.50-1.19	0.239
isotype IgG	0.79	0.59-1.04	0.091
isotype IgA	0.54	0.35-0.82	0.004
isotype BJ	0.68	0.31-1.47	0.326
WHO PS 0-1	0.73	0.52-1.04	0.08
WHO PS 2-4	0.87	0.59-1.28	0.477
CR + VGPR	1.05	0.71-1.56	0.81
PR	0.55	0.39-0.78	0.001
<PR	0.74	0.47-1.14	0.74

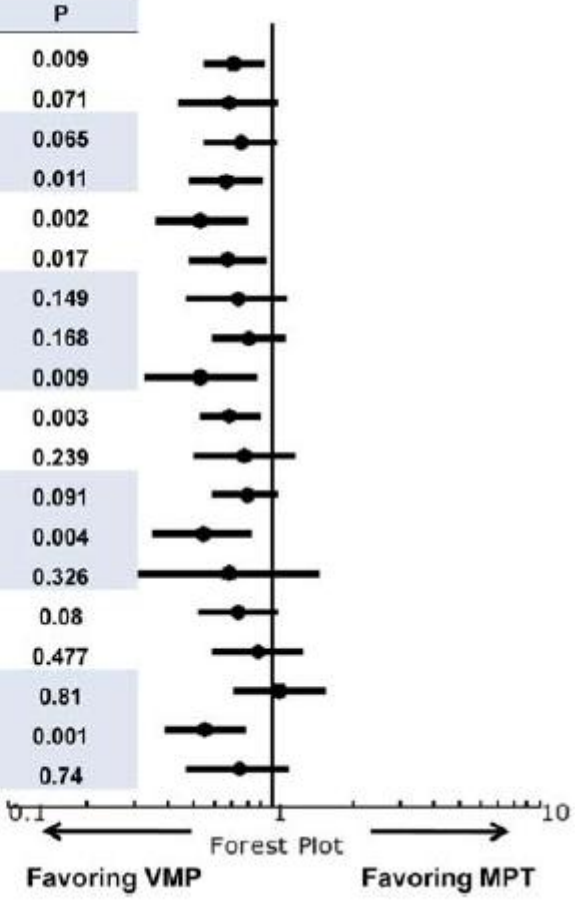


Figure 2.

Cox univariate analyses of progression-free survival. Analyses of the progression-free survival among subgroups of patients, as defined according to baseline demographic. Hazard ratios lower than 1 indicate a lower risk of progression. The I bars represent 95% confidence intervals. VMP, bortezomib, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; HR, hazard ratio; CI, confidence interval; DS, Durie and Salmon; ISS, International Staging System; BJ, Bence Jones; PS, performance status; CR, complete response; VGPR, very good partial response; PR, partial response.

Table 4. Multivariate Analyses (Cox Model) of Overall Survival and Progression-Free Survival

	Overall survival						Progression-free survival					
		Univariate analysis			Multivariate analysis No. of cases = 461		Univariate analysis			Multivariate analysis No of cases = 463		
	No of cases	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age at diagnosis (≥75 vs. <75 yrs)	230/360	1. 28	0.58–2.83	0.535				1.31	0.71–2.44	0.386			
Gender (male vs. female)	312/278	1.14	0.84–1.55	0.390				1.05	0.83–1.33	0.692			
Chemotherapy regimen (VMP vs. MPT)	296/294	0.44	0.32–0.59	<0.001	0.38	0.25–0.59	<0.001	0.65	0.51–0.82	<0.001	0.54	0.37–0.80	0.002
Durie-Salmon stage (III vs. I+II)		1.23	0.89–1.71	0.214				1.37	1.05–1.78	0.022	1.13	0.82–1.57	0.451
ISS score				0.189#			0.888#			0.249#			
II vs. I	288/162	1.51	0.97–2.34	0.068	1.14	0.67–1.93	0.625	1.27	0.93–1.73	0.130			
III vs. I	140/162	1.51	0.70–3.23	0.294	1.13	0.44–2.90	0.807	1.04	0.55–1.97	0.902			
ECOG PS (≥2 vs. 0–1)	185/272	1.35	0.96–1.89	0.084	1.42	0.98–2.07	0.068	1.44	1.10–1.88	0.008	1.57	1.12–2.20	0.009
Serum creatinine (>1.2 vs. ≤1.2 mg/dl)	172/408	0.94	0.66–1.34	0.733				0.92	0.69–1.22	0.562			
Serum calcemia (>2.35 vs. ≤2.35 mg/dl)	292/264	1.14	0.84–1.57	0.399				1.05	0.83–1.34	0.680			
Ig isotypes				0.582#						0.486#			
IgA vs. IgG	146/384	1.18	0.84–1.66	0.348				1.16	0.89–1.51	0.271			
BJ vs. IgG	51/384	0.92	0.51–1.65	0.781				0.94	0.61–1.46	0.781			
Best response[a]				<0.001#			<0.001#			<0.001#			<0.001
VGPR vs. CR	112/99	4.64	1.91–11.31	0.001	9.74	3.08–30.83	<0.001	5.03	2.77–9.14	<0.001	11.18	4.61–27.10	<0.001
PR vs. CR	222/99	13.19	4.32–40.26	<0.001	38.41	8.14–181.40	<0.001	11.77	5.21–26.21	<0.001	39.67	11.60–135.71	<0.001
<PR vs. CR	135/99	46.69	12.25–177.98	<0.001	170.12	26.49–1092.6	<0.001	32.81	12.03–89.51	<0.001	97.77	22.19–430.85	<0.001

[a] Treated as a time-dependent variable; # overall p-values for the whole variable with its dichotomous dummies accommodating its multinomial modalities.

All Cox models were estimated stratifying the cohort on k-means cluster.

ISS, International Staging System; PS, Performance status; D&S, Durie and Salmon staging system; CI, Confidence Interval; HR, Hazard Ratio; BJ, Bence Jones; VMP, bortezomib-melphalan-prednisone; MPT, melphalan-prednisone-thalidomide; CR, complete response; VGPR, very good partial response PR, partial response.

Overall survival

At time of analysis, 197 patients (33%) had died. In the entire population, the median OS was 61.9 months (IQR, 26.5–79.7). Median OS was 79.7 months in the VMP group and 45.1 months in the MPT group ($P < 0.001$). The three-year OS was 77.8% in VMP cases and 58.5% in MPT cases (Fig. 1, Panel B). VMP led to a 56% reduced risk of death compared with MPT. VMP led to a statistically significant benefit in terms of OS in all subgroups defined by gender, Durie-Salmon stage, ISS, creatinine level, PS, age <75 years, IgG or IgA isotype, and by achievement of ≥VGPR or PR (Fig. 3). Moreover, although we observed in patients ≥75 years a positive trend for VMP cases, in this setting VMP did not statistically impact on OS compared with MPT (HR 0.63; 95% CI 0.38–1.02; $P = 0.061$). However, a landmark analysis of OS for 318 relapsed patients, calculated from time of relapse, showed a significant longer survival in favor of VMP (three-year OS rate was 61.7 in VMP cases and 24.8% in MPT cases; HR 0.51; 95% CI, 0.35–0.75; $P < 0.0001$). Overall, age ≥75 years did not increase the risk of death in the subgroup of patients receiving either VMP (HR 2.06; 95% CI, 0.69–6.16; $P = 0.198$) or MPT (HR 0.62; 95% CI 0.14–2.85; $P = 0.54$). Upon multivariate analysis, VMP treatment, quality of response, and PS resulted in independent predictors of better outcome (Table 4). When patients were stratified by trial, VMP cases in PETHEMA-GEM05MAS65 showed a statistically longer OS than MPT cases in NMSG and HOVON-49 trials, but not different than cases treated with MPT in GISMM-2001 and TMSG trials, while cases treated with VMP in GIMEMA-MM0305 showed a statistically better OS than cases treated with MPT in HOVON-49, NMSG, TMSG, and GISMM-2001 trials (Supporting Information Figure 1, Panel B).

Variable	HR	95% CI	P
age<75	0.36	0.24-0.52	<0.001
age>75	0.63	0.38-1.02	0.061
male	0.42	0.28-0.63	<0.001
female	0.47	0.30-0.74	0.001
DS I+II	0.36	0.21-0.64	<0.001
DS III	0.47	0.30-0.73	0.001
ISS I	0.26	0.12-0.56	0.001
ISS II	0.51	0.33-0.77	0.002
ISS III	0.47	0.28-0.80	0.005
creat < 1.2	0.42	0.29-0.60	<0.001
creat > 1.2	0.53	0.31-0.91	0.021
isotype IgG	0.5	0.35-0.74	<0.001
isotype IgA	0.32	0.17-0.57	<0.001
isotype BJ	0.4	0.14-1.14	0.087
WHO PS 0-1	0.43	0.24-0.78	<0.001
WHO PS 2-4	0.29	0.17-0.49	<0.001
CR + VGPR	0.28	0.14-0.58	0.001
PR	0.44	0.27-0.72	0.001
<PR	0.68	0.43-1.08	0.102

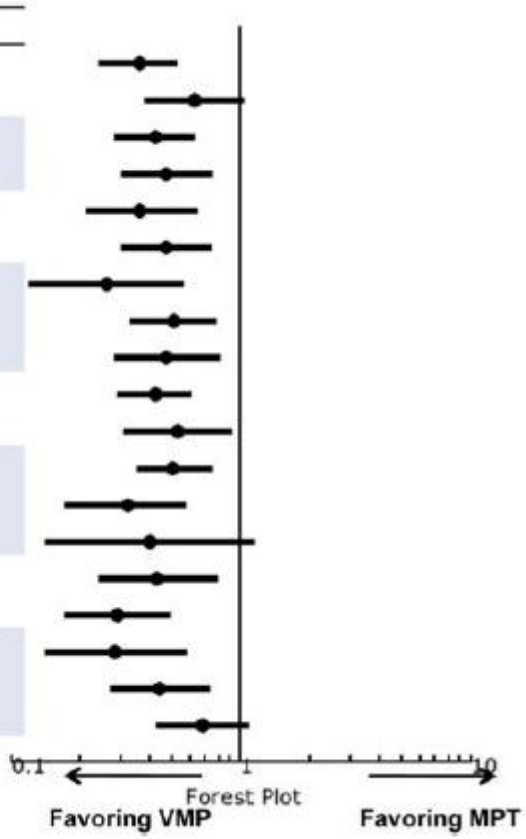


Figure 3.

Cox univariate analyses of overall survival. Analyses of overall survival among subgroups of patients, as defined according to baseline demographics. Hazard ratios lower than 1 indicate a lower risk of progression. The I bars represent 95% confidence intervals. VMP, bortezomib, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; HR, hazard ratio; CI, confidence interval; DS, Durie and Salmon; ISS, International Staging System; BJ, Bence Jones; PS, performance status; CR, complete response; VGPR, very good partial response; PR, partial response.

Frequency of adverse events

Rates of treatment-related death were similar between VMP and MPT: 18 patients (5.8%) died in the VMP group and 22 (7%) in the MPT ($P = 0.51$) group with the major cause of death being infection (five patients in VMP and six patients in MPT). The incidence of at least one grade 3–4 hematologic AE was significantly higher in patients receiving VMP compared with MPT (42.6% vs. 31.9%; $P = 0.008$). Grade 3–4 thrombocytopenia was slightly more frequent in VMP cases (11.9% vs. 7.4%; $P = 0.077$). The incidence of at least one grade 3–4 non-hematologic AE was significantly lower in VMP patients compared with MPT (31.9% vs. 42.6%; $P = 0.008$). Consistently, grade 3–4 cardiac complications were fewer in VMP cases (3.2% vs. 9%; $P = 0.004$). Similarly, VMP was associated with a lower incidence of severe infections (8.1% vs. 14.8%; $P = 0.011$) and severe dermatologic events (1.6% vs. 5.5%; $P = 0.015$) compared with MPT therapy. In the VMP group, 16 cases (5%) of deep vein thrombosis (DVT) occurred; in the MPT group, 21 cases (7%) of DVT and 5 cases (2%) of pulmonary embolism were detected ($P = 0.11$). A slightly higher rate of grade 3–4 sensory neuropathy and/or neuralgia was reported in VMP cases (11.3% vs. 7.1%; $P = 0.095$). The incidence of other severe nervous system events was significantly lower in VMP patients compared to MPT (2.3% vs. 6.8%; $P = 0.011$). The proportion of patients requiring therapy interruption was significantly different in the two groups (VMP 17% versus MPT 33%, $P = 0.0001$).

Discussion

In MM patients, survival varies according to host and disease characteristics. Treatment choice is crucial in the improvement of response rate and survival, preserving quality of life. Over the last decade, the use of thalidomide, bortezomib, and lenalidomide significantly prolonged survival [22]. However, this advantage was much less pronounced in patients >60 years, while no survival improvement was observed in patients >70 years [23, 24]. This difference may be due to frailty, co-morbidities, or disabilities, which often limit the management of elderly patients [16]. Because vulnerable elderly patients are underrepresented in clinical trials, our study may be less representative of the overall elderly population. Nevertheless, this is the largest analysis conducted on elderly MM patients to date.

In this retrospective case-matched study, data from 590 untreated MM patients receiving VMP or MPT were analyzed. VMP was associated with a significant reduced risk of both progression and death compared with the MPT, independently of sex, ISS, PS, or serum creatinine. Two major limitations should be considered when evaluating the net impact of VMP on OS. First, efficacy data of post-progression treatments are not available, and, second, the post progression therapeutic armamentarium is potentially different since the trials were conducted in different periods. However, a landmark analysis of OS for 318 relapsed patients, calculated from the time of relapse, showed a significant better prognosis for the VMP group.

Older patients commonly have more adverse prognostic factors and shorter survival [25]. In the meta-analysis comparing MP with MPT [3], as well as in the VISTA study comparing MP with VMP [10-12], survival was worse in patients ≥75 years. In our study, age ≥75 years did not significantly increase the risk of death in patients receiving either VMP or MPT. Moreover, although a positive trend for VMP was observed, the type of therapy did not significantly impact OS in patients ≥75 years. These results should be interpreted with caution given the good fitness and the limited number of very elderly patients in our population (30% of the patients analyzed). This study suggests that VMP could be considered the first treatment choice in patients between 65 and 75 years, while we cannot conclude likewise for very elderly patients (≥75 years) since only a positive trend in terms of PFS and OS in favor of VMP was observed. Traditionally, PS measured the fitness of patients, but its role as a unique marker of functional status needs to be revised. The presence of co-morbidities is also a significant concern. In this analysis, poor PS cases represented only 30% of the whole study population. The benefit of VMP in terms of OS was also observed in this subset of patients, although the lack of information about co-morbidity and the number of unavailable PS values limits our understanding of the impact of patients' characteristics on clinical outcome.

Similarly, although both thalidomide and bortezomib pharmacokinetics are not affected by renal impairment and no dose reduction is required, our data showed that the benefit of VMP in terms of OS is independent of creatinine values. These results further support the recent IMWG consensus statement recommending VMP as first-line treatment in elderly patients with renal failure [26].

The ISS classification [27] along with cytogenetic status [28] is the most relevant prognostic factor in MM. ISS still remains an independent predictor of outcome and treatment of high-risk patients remains unsatisfactory. However, in our analysis the OS benefit of VMP was observed in all patient subgroups defined by ISS. Unfortunately, cytogenetic data were insufficient and could not be used to better dissect its prognostic impact.

In line with our results, several studies have recently emphasized the role of CR as an independent predictor of longer survival [29-31]. In a recent retrospective study on 1,175 patients, CR achievement was associated with improved OS, with three-year OS rates of 91% in CR patients and 67–70% in those in VGPR or PR [30].

Both the toxicity profiles of VMP and MPT and treatment-related deaths were similar in the two groups. The overall incidence of grade 3–4 hematologic AEs was significantly higher in VMP patients, especially thrombocytopenia. Conversely, the incidence of infections and dermatologic and cardiac complications was higher in MPT patients. Therefore, cardiologic workup before starting thalidomide is appropriate to detect asymptomatic cardiologic abnormalities. A more careful assessment of fevers of unknown origin and prompt administration of antibiotic prophylaxis might reduce the risk of infection. The incidence of grade 3–4 sensory neuropathy and/or neuralgia was slightly higher in the VMP group; conversely, MPT patients showed a higher incidence of other severe nervous system events. Subcutaneous bortezomib could further improve the bortezomib toxicity profile [32]. Finally, the incidence of thromboembolism was 5% in VMP patients and 9% in MPT patients.

To date, no randomized trial has directly compared VMP and MPT. A recent indirect comparison of VMP vs. MPT showed no differences between the two regimens for all outcomes, but a significant CR benefit with lower toxicity profile favoring VMP [33]. Given the limits of a retrospective analysis and the lack of relevant data, such as post-relapse treatment and role of maintenance, co-morbidity and cytogenetics, this is the first direct comparison between the two schedules. Nevertheless, our data should be considered in the light of obvious heterogeneity in the patient

population and treatment regimens among different trials analyzed in this study, including variability in dosing, duration of treatment, and maintenance.

In light of our findings, should we recommend VMP over MPT? It is difficult to draw a definitive conclusion given the retrospective design of our study. Moreover, our analysis was an indirect comparison of treatment, given that patients in MPT and VMP came from completely different trials. Despite this limit, we analyzed data derived from the most important European randomized trials [4, 7, 8, 13, 14], matched by age, albumin, and beta2-microglobulin levels, thereby shrinking influences of potential prognostic imbalances. We found that VMP is associated with better quality of response and longer PFS and OS in comparison with MPT. A critical point could be represented by maintenance therapy. Thalidomide maintenance was planned in 3/4 MPT protocols (HOVON-49 [8], GISMM-2001 [4], and NMSG [7] trials) we examined; conversely only the PETHEMA-GEM05MAS65 [14] trial foresaw bortezomib maintenance, and this further supports VMP superiority. Finally, VMP's positive impact on PFS was further supported by two ad hoc sub-analyses in which trials with or without maintenance were evaluated separately by both univariate and multivariate analysis. Furthermore, it must be considered that the VMP arm observed a higher rate of cases with worse PS than the MPT arm. Considering the favorable toxicity profile and the efficacy of both VMP and MPT, along with the increased life expectancy of the general population and the enhanced PS of numerous old patients, clinicians could move from a more palliative therapy to a more intensive therapeutic approach in elderly MM patients. Uncertainty may remain in the selection of the more appropriate treatment in this setting; our results may help physicians make a more informed choice in favor of VMP.

Author Contributions

Conception and design: Fortunato Morabito, Sara Bringhen, Alessandra Larocca, Maris Victoria Mateos, Roberto Passera, Mario Boccadoro, Antonio Palumbo,Massimo Offidani. Provision of study materials or patients: Fortunato Morabito, Sara Bringhen, Alessandra Larocca, Pierre Wijermans, Maria Victoria Mateos, Peter Gimsing, Carla Mazzone, Daniela Gottardi, Paola Omedè, Sonja Zweegman, Juan José Lahuerta, Renato Zambello, Pellegrino Musto, Valeria Magarotto, Martijn Schaafsma, Albert Oriol, Gunnar Juliusson, Chiara Cerrato, Lucio Catalano, Massimo Gentile, Ana Isabel Turel, Anna Marina Liberati, Maide Cavalli, Davide Rossi, Roberto Passera, Meral Beksac, Michele Cavo, Anders Waage, Jesus San Miguel, Mario Boccadoro, Pieter Sonneveld, Antonio Palumbo, Massimo Offidani. Collection and assembly of data: Fortunato Morabito, Sara Bringhen, Alessandra Larocca, Pierre Wijermans, Maria Victoria Mateos, Peter Gimsing, Carla Mazzone, Daniela Gottardi, Paola Omedè, Sonja Zweegman, Juan José Lahuerta, Renato Zambello, Pellegrino Musto, Valeria Magarotto, Martijn Schaafsma, Albert Oriol, Gunnar Juliusson, Chiara Cerrato, Lucio Catalano, Massimo Gentile, Ana Isabel Turel, Anna Marina Liberati, Maide Cavalli, Davide Rossi, Roberto Passera, Meral Beksac, Michele Cavo, Anders Waage, Jesus San Miguel, Mario Boccadoro, Pieter Sonneveld, Antonio Palumbo, Massimo Offidani. Data analysis and interpretation: Fortunato Morabito, Sara Bringhen, Massimo Gentile, Alessandra Larocca, Paola Omedè, Valeria Magarotto, Chiara Cerrato, Roberto Passera, Stefano Rosso, Mario Boccadoro, Antonio Palumbo. Manuscript writing: Fortunato Morabito, Sara Bringhen, Alessandra Larocca, Pierre Wijermans, Maria Victoria Mateos, Peter Gimsing, Carla Mazzone, Daniela Gottardi, Paola Omedè, Sonja Zweegman, Juan José Lahuerta, Renato Zambello, Pellegrino Musto, Valeria Magarotto, Martijn Schaafsma, Albert Oriol, Gunnar Juliusson, Chiara Cerrato, Lucio Catalano, Massimo Gentile, Ana Isabel Turel, Anna Marina Liberati, Maide Cavalli, Davide Rossi, Roberto Passera, Meral Beksac, Michele Cavo, Anders Waage, Jesus San Miguel, Mario Boccadoro, Pieter Sonneveld, Antonio Palumbo, Massimo Offidani. Final approval of manuscript: Fortunato Morabito, Sara Bringhen, Alessandra Larocca, Pierre Wijermans, Maria Victoria Mateos, Peter Gimsing, Carla Mazzone, Daniela Gottardi, Paola Omedè, Sonja Zweegman,

Juan José Lahuerta, Renato Zambello, Pellegrino Musto, Valeria Magarotto, Martijn Schaafsma, Albert Oriol, Gunnar Juliusson, Chiara Cerrato, Lucio Catalano, Massimo Gentile, Ana Isabel Turel, Anna Marina Liberati, Maide Cavalli, Davide Rossi, Roberto Passera, Meral Beksac, Michele Cavo, Anders Waage, Jesus San Miguel, Mario Boccadoro, Pieter Sonneveld, Antonio Palumbo, Massimo Offidani.

Acknowledgments

The authors thank the patients who took part in the studies, the nurses De Lazzer Tiziana and Tresoldi Ornella, the data managers Federica Leotta and Tiziana Marangon, and the editorial assistant Giorgio Schirripa.

References

1. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. J Clin Oncol 1998;12:3832–3842.
2. Kapoor P, Rajkumar SV, Dispenzieri A, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: A meta-analysis. Leukemia 2011; 25:689–696.
3. Fayers PM, Palumbo A, Hulin C, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: Meta-analysis of 1685 individual patient data from 6 randomized clinical trials. Blood 2011;118:1239–1247.
4. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: Randomised controlled trial. Lancet 2006;367:825–831.
5. 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 randomized trial. Lancet 2007;370:1209–1218.
6. 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 2009;27:3664–3670.
7. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116:1405–1412.
8. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: The HOVON 49 study. J Clin Oncol 2010;28:3160–3166.
9. Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: Results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol 2011;86:16–22.
10. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906–917.
11. Mateos MV, Richardson PG, Schlag R, et al. 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. J Clin Oncol 2010;28:2259–2266.
12. San Miguel JF, Schlag R, Khuageva NK, et al. Continued overall survival benefit after 5 years' follow-up with bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) in patients with previously untreated multiple myeloma, and no increased

risk of second primary malignancies: Final results of the phase 3 VISTA trial. Blood (ASH Annual Meeting Abstracts) 2011;118:476.
13. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol 2010;28:5101–5109.
14. Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial. Lancet Oncol 2010;11:934–941.
15. Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once weekly bortezomib in multiple myeloma patients. Blood 2010;116:4745–4753.
16. Palumbo A, Bringhen S, Ludwig H, et al. Personalized therapy in multiple myeloma according to patient age and vulnerability: A report of the European Myeloma Network (EMN). Blood 2011;118:4519–4529.
17. Hartigan JA, Wong MA. A K-means clustering algorithm. Appl Stat 1979;28:100–108.
18. 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. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115–1123.
19. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–1473.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
21. Cox DR. Regression model and life tables. J R Stat Soc B 1972;34:187–220.
22. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516–2520.
23. Brenner H, Gondos A, Pulte D. Recent major improvements in long-term survival of younger patients with multiple myeloma. Blood 2008;111:2521–2526.
24. Schaapveld M, Visser O, Siesling S, et al. Improved survival among younger but not among older patients with multiple myeloma in the Netherlands, a population-based study since 1989. Eur J Cancer 2010;46:160–169.
25. Ludwig H, Durie BG, Bolejack V, et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: An analysis of 10 549 patients from the International Myeloma Working Group. Blood 2008;111:4039–4047.
26. Dimopoulos MA, Terpos E, Chanan-Khan A, et al. Renal impairment in patients with multiple myeloma: A consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol 2010;28:4976–4984.
27. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412–3420.
28. Hervé AL, Florence M, Philippe M, et al. Molecular heterogeneity of multiple myeloma: pathogenesis, prognosis, and therapeutic implications. J Clin Oncol 2011;29:1893–1897.
29. Chanan-Khan AA, Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. J Clin Oncol 2010;28:2612–2624.
30. Harousseau JL, Palumbo A, Richardson PG, et al. Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. Blood 2010;116:3743–3750.

31. Gay F, Larocca A, Wijermans P, et al. Complete response correlates with long-term progression free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. Blood 2011;117:3025–3031.
32. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, noninferiority study. Lancet Oncol 2011;12:431–440.
33. Kumar A, Hozo I, Wheatley K, et al. Thalidomide versus bortezomib based regimens as first-line therapy for patients with multiple myeloma: A systematic review. Am J Hematol 2011;86:18–24.