VOLUME 27 · NUMBER 36 · DECEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

VMP (Bortezomib, Melphalan, and Prednisone) Is Active and Well Tolerated in Newly Diagnosed Patients With Multiple Myeloma With Moderately Impaired Renal Function, and Results in Reversal of Renal Impairment: Cohort Analysis of the Phase III VISTA Study

Meletios A. Dimopoulos, Paul G. Richardson, Rudolf Schlag, Nuriet K. Khuageva, Ofer Shpilberg, Efstathios Kastritis, Martin Kropff, Maria T. Petrucci, Michel Delforge, Julia Alexeeva, Rik Schots, Tamás Masszi, Maria-Victoria Mateos, William Deraedt, Kevin Liu, Andrew Cakana, Helgi van de Velde, and Jesús F. San Miguel

From the Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, School of Medicine, Athens, Greece; Dana-Farber Cancer Institute, Boston, MA; Johnson & Johnson Pharmaceutical Research & Development LLC, Raritan, NJ; Praxisklinik Dr Schlag, Würzburg; University of Münster, Münster, Germany; SP Botkin Moscow City Clinical Hospital, Russian Federation, Rabin Medical Center, Petah-Tiqva, Israel; University La Sapienza, Rome, Italy; Myeloma Study Group Belgian Hematological Society, Brussels; Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium; St Petersburg Clinical City Hospital, St Petersburg, Russia; St István and St László Hospital of Budapest, Budapest, Hungary; and the Hospital Universitario Salamanca, Centro de Investigación del Cáncer, Instituto de Biología Molecular y Celular del Cáncer (Universidad de Salamance, Consejo Superior de Investigaciones Cientificas), Salamanca, Spain.

Submitted January 27, 2009; accepted July 23, 2009; published online ahead of print at www.jco.org on October 26, 2009.

Supported by Johnson & Johnson Pharmaceutical Research & Development LLC and Millennium Pharmaceuticals.

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

Clinical Trials repository link available on JCO.org.

Corresponding author: Meletios A. Dimopoulos, MD, Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, School of Medicine, Athens, Greece; e-mail: mdimop@med.uoa.gr.

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2736-6086/$20.00

DOI: 10.1200/JCO.2009.22.2232

ABSTRACT

Purpose
To assess bortezomib plus melphalan and prednisone (VMP) and melphalan and prednisone (MP) in previously untreated patients with multiple myeloma (MM) with renal impairment enrolled on the phase III VISTA study, and to evaluate renal impairment reversibility.

Patients and Methods
Patients received nine 6-week cycles of VMP (bortezomib 1.3 mg/m^2, melphalan 9 mg/m^2, prednisone 60 mg/m^2) or MP. Patients with serum creatinine higher than 2 mg/dL were excluded.

Results
In the VMP/MP arms, 6%/4%, 27%/30%, and 67%/66% of patients had baseline glomerular filtration rate (GFR) of ≤ 30, 31 to 50, and higher than 50 mL/min, respectively. Response rates were higher and time to progression (TTP) and overall survival (OS) longer with VMP versus MP across renal cohorts. Response rates with VMP and TTP in both arms did not appear significantly different between patients with GFR ≤ 50 or higher than 50 mL/min; OS appeared somewhat longer in patients with normal renal function in both arms. Renal impairment reversal (baseline GFR < 50 improving to > 60 mL/min) was seen in 49 (44%) of 111 patients receiving VMP versus 40 (34%) of 116 patients receiving MP. By multivariate analysis, younger age (< 75 years; $P = .006$) and less severe impairment (GFR ≥ 30 mL/min; $P = .027$) were associated with higher reversal rates. In addition, treatment with VMP approached significance ($P = .07$). In both arms, rates of grade 4 and 5 adverse events (AEs) and serious AEs appeared higher in patients with renal impairment; with VMP, rates of discontinuations/bortezomib dose reductions due to AEs did not appear affected.

Conclusion
VMP is a feasible, active, and well-tolerated treatment option for previously untreated patients with MM with moderate renal impairment, resulting in 44% renal impairment reversal.

J Clin Oncol 27:6086-6093. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Renal impairment is a major complication of multiple myeloma (MM),[1,2] and is most frequently due to light chain tubular cast nephropathy.[2] Approximately 30% of newly diagnosed patients with MM present with serum creatinine (SCr) ≥ 1.5 mg/dL,[1,3] and approximately 20% have SCr ≥ 2.0 mg/dL.[4-7] Glomerular filtration rate (GFR) is a more accurate measure of renal function, and may be calculated from SCr using the Cockcroft-Gault formula.[8]

Renal impairment in MM is associated with poorer outcomes, including lower response to treatment and shorter overall survival (OS), compared with normal renal function.[3,5,6,9] Renal impairment may also adversely affect outcomes due to lower recommended starting doses or the need for dose reductions or interruptions with some drugs,[2,10,11] and higher rates of associated comorbidities and complications compared with patients with normal renal function.[2] In addition, it is associated with more advanced disease[5,12] and higher tumor burden.[12]

Early effective treatment can lead to renal function improvement; renal impairment is reversible with anti-MM treatment in up to 73% of patients, depending on how reversibility is defined.[3-5,13,14] In some studies, renal impairment reversal has been associated with prolonged survival versus irreversible impairment.[3,5,14,15]

New highly active, tolerable treatment options are required for patients with MM with renal impairment. Previous studies have shown bortezomib to be effective in patients with MM with various degrees of renal impairment, including dialysis dependence.[15-23] Bortezomib pharmacokinetics are not affected by renal impairment, and so no starting dose reductions are required.[24] Bortezomib is approved for first-line treatment of MM based on the international, phase III VELCADE as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone (VISTA) study in previously untreated patients with MM; bortezomib plus melphalan and prednisone (VMP) was superior to melphalan and prednisone (MP) across all efficacy end points, including response rates, time to progression (TTP), and overall survival (OS).[25] A previous study of MP found lower response rates and significantly shorter survival in patients with renal impairment; the authors suggested that melphalan dose reductions may be required due to elevated rates of hematologic toxicity.[10] Therefore, this cohort analysis of VISTA was conducted to assess efficacy and safety of VMP and MP in patients with renal impairment, and to evaluate renal impairment reversibility.

PATIENTS AND METHODS

Patients and Study Design

The VISTA study design has been reported previously.[25] Briefly, patients with previously untreated MM ineligible for high-dose therapy were randomly assigned to receive nine 6-week cycles of VMP (bortezomib [VELCADE, Millennium Pharmaceuticals, Cambridge, MA, and Johnson & Johnson Pharmaceutical Research & Development LLC, Raritan, NJ] 1.3 mg/m^2, 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^2 and prednisone 60 mg/m^2, days 1 to 4, cycles 1 to 9; n = 344) or MP (n = 338). Random assignment was stratified by baseline β_2-microglobulin, albumin, and region. Patients with SCr higher than 2 mg/dL (approximately 20% of MM patients at diagnosis[4-7]) were excluded, due to melphalan use, as were patients with grade $\geq$ 2 peripheral sensory neuropathy/neuropathic pain according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, due to bortezomib use.

Patients discontinued treatment due to progressive disease (PD) or unacceptable toxicity, or by patient/investigator decision. Dose reductions were required for excessive toxicity. For grade 3/4 renal impairment, treatment was held until recovery to grade 1/baseline; for grade lower than 3 renal impairment with SCr higher than 2 mg/dL, melphalan dose was temporarily reduced (9.0 $\rightarrow$ 4.5 mg/m^2) until SCr was $\leq$ 2 mg/dL.

Response was determined by prespecified computer algorithm and progression assessed by investigators every 3 weeks for 54 weeks, then every 8 weeks until PD, according to European Group for Blood and Marrow Transplantation criteria,[26] using serum/urine M-protein measurements and other assessments as required. Patients were then observed at least every 12 weeks. Safety was evaluated until 30 days after the last dose of study drug; adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. SCr was assessed locally every 3 weeks during treatment and at the end-of-treatment visit. Review boards at all participating institutions approved the study, which was conducted according to the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Renal Cohort Analysis

Patients in both arms were analyzed in renal impairment cohorts defined by baseline estimated GFR, based on calculated[8] creatinine clearance. Normal renal function was defined as GFR higher than 50 mL/min; renal impairment (GFR $\leq$ 50 mL/min) was subdivided as moderate (31 to 50 mL/min) or severe ($\leq$ 30 mL/min). Cohort definitions were based on revised[27] stratification by National Kidney Foundation Practice Guidelines for Chronic Kidney Disease,[28] but with a more stringent GFR cutoff for defining renal impairment ($\leq$ 50 v $\leq$ 60 mL/min) in these elderly patients, in whom estimated GFR may be lowered despite normal SCr levels. Response rates were determined using initial VISTA data[25] in response-evaluable patients in the renal cohorts. TTP was analyzed using initial data (median follow-up, 16.3 months)[25] and OS using updated data.

Analysis of Renal Impairment Reversibility

Reversibility of renal impairment was defined as improvement in GFR from lower than 50 mL/min at baseline to higher than 60 mL/min on treatment. Renal function improvement was evaluated in terms of GFR increases of $\geq$ 20 mL/min from baseline, and as renal responses, based on definitions presented by Ludwig et al[21] (complete response [CR]^{renal}: baseline GFR $<$ 50 mL/min improving to $\geq$ 60; partial response [PR]^{renal}: baseline GFR $<$ 15 improving to 30 to $<$ 60; minimal response [MR]^{renal}: baseline GFR $<$ 15 improving to 15 to $<$ 30 or baseline GFR 15 to $<$ 30 improving to 30 to $<$ 60). Factors associated with renal impairment reversal were assessed by univariate and multivariate analyses. OS and safety profile were compared by arm between patients with baseline GFR lower than 50 mL/min who did or did not achieve renal impairment reversal.

Statistical Analysis

Response rates were compared between arms by renal cohort using the Mantel-Haenszel estimate of common odds ratio (OR) for stratified tables, with P values determined by Cochran Mantel-Haenzel χ^2 test. TTP, OS, and time to renal impairment reversal distributions were estimated by Kaplan-Meier methodology. Hazard ratios (HRs) for comparisons between arms by cohort were based on stratified Cox's regression analyses with treatment as explanatory variable; P values were based on stratified log-rank tests, except where indicated.

RESULTS

Patient Characteristics

In total, 340 and 337 patients randomly assigned to VMP and MP, respectively, received at least one dose of study drug and were included in this analysis. Approximately one third of the patients on each arm presented with impaired renal function, predominantly moderate impairment; 19 (6%), 92 (27%), and 229 (67%) patients receiving VMP, and 15 (4%), 101 (30%), and 221 (66%) receiving MP, had GFR $\leq$ 30, 31 to 50, and more than 50 mL/min, respectively; 0 and 2 patients receiving VMP and MP, respectively, had GFR lower than 15 mL/min. Baseline characteristics appeared similar between arms overall and between respective renal cohorts (Table 1). The renal impairment cohorts, notably the severe impairment cohorts, appeared to include higher proportions of patients with International Staging System (ISS) stage III disease and baseline β_2-microglobulin higher than 5.5 mg/L, due to β_2-microglobulin reflecting both tumor burden and renal function.

Efficacy

Overall response and CR rates were higher with VMP versus MP (Table 2), with ORs consistently in favor of VMP, including in all patients with renal impairment (overall: OR, 2.458, P = .001; CR: OR, 7.060, P $<$ .00001) or normal renal function (overall: OR, 6.085; P $<$ .00001; CR: OR, 15.851; P $<$ .00001), in patients with moderate

Table 1. Baseline Patient and Disease Characteristics in the VMP and MP Arms and by Renal Cohort

Characteristic	VMP Arm					MP Arm				
		Renal Cohort, GFR, mL/min					Renal Cohort, GFR, mL/min			
	Total (n = 340)	≤ 30 (n = 19)	31-50 (n = 92)	≤ 50 (n = 111)	> 50 (n = 229)	Total (n = 337)	≤ 30 (n = 15)	31-50 (n = 101)	≤ 50 (n = 116)	> 50 (n = 221)
Median age, years	71	76	75	75	70	71	76	75	75	70
Male, %	51	26	48	44	54	49	27	39	37	56
White, %	88	84	85	85	90	87	93	84	85	88
Asian, %	10	11	14	14	8	11	7	15	14	9
KPS ≤ 70%, %	36	63	40	44	32	33	33	41	40	29
ISS Stage III, %	34	84	58	62	21	34	80	52	56	22
Median β_2M, mg/L	4.2	8.2	6.15	6.3	3.5	4.3	9.0	5.7	6.0	3.7
β_2M > 5.5 mg/L, %	33	84	54	59	20	33	73	51	54	22
Median albumin, g/dL	3.3	3.3	3.2	3.2	3.3	3.3	3.2	3.2	3.2	3.3
Albumin ≥ 3.5 g/dL, %	42	42	43	43	41	38	40	35	36	39

Abbreviations: VMP, bortezomib plus melphalan and prednisone; MP, melphalan and prednisone; GFR, glomerular filtration rate; KPS, Karnofsky performance status; ISS, International Staging System; β_2M, β_2 microglobulin.

renal impairment (overall: OR, 2.340; $P = .0053$; CR: OR, 8.647; $P < .0001$), and in the small cohorts with severe renal impairment (overall: OR, 3.571; $P = .1205$; CR: OR, 3.231; $P = .2268$). Within the VMP arm, overall response and CR rates appeared similar between cohorts. Median time to first response with VMP appeared similarly rapid across renal cohorts and was consistently quicker compared with MP. Median duration of response with VMP also appeared generally longer compared with MP, and was longer in patients with normal renal function versus renal impairment in both arms.

TTP was longer with VMP than with MP, with HRs consistently in favor of VMP, in patients with severe (HR, 0.209; $P = .1381$), moderate (HR, 0.546; $P = .0201$), or any renal impairment (HR, 0.517; $P = .0057$), and in patients with normal renal function (HR, 0.481; $P < .0001$). TTP appeared similar between patients with renal impairment and those with normal renal function with both VMP and MP (Fig 1A). After median follow-up of 25.9 months, OS was also longer with VMP versus MP, with HRs consistently in favor of VMP, in patients with severe (HR, 0.63; $P = .4687$), moderate (HR, 0.611; $P = .0615$), or any renal impairment (HR, 0.699; $P = .1242$), and in patients with normal renal function (HR, 0.636; $P = .0235$; Table 2). OS appeared somewhat longer in patients with normal renal function versus those with renal impairment with both VMP and MP (Fig 1B). At data cutoff, 129 (38%) and 194 (57%) of patients in the VMP and MP arms had received subsequent therapy; among MP patients with GFR ≤ 50 and higher than 50 mL/min, 28 (24%) and 56 (25%), respectively, had received subsequent bortezomib-containing therapy (48% and 41%, respectively, of patients receiving any subsequent therapy).

Reversal of Renal Impairment

The rate of renal impairment reversal was higher with VMP, with 49 (44%) of 111 patients with baseline GFR lower than 50 mL/min improving to higher than 60 mL/min on treatment, compared with 40 (34%) of 116 patients on the MP arm. With VMP, seven (37%) of 19 patients with GFR lower than 30 mL/min and 42 (46%) of 92 patients with GFR 30—less than 50 mL/min experienced renal impairment

Table 2. Response Rate, TTP, and OS in the VMP and MP Arms and by Renal Cohort

Measure	VMP Arm					MP Arm				
		Renal Cohort, GFR, mL/min					Renal Cohort, GFR, mL/min			
	Total (n = 340)	≤ 30 (n = 19)	31-50 (n = 92)	≤ 50 (n = 111)	> 50 (n = 229)	Total (n = 337)	≤ 30 (n = 15)	31-50 (n = 101)	≤ 50 (n = 116)	> 50 (n = 221)
Response-evaluable, n	337	19	92	111	226	331	15	99	114	217
Response rate, %	71	74	67	68	72	35	47	45	46	29
CR rate, %	30	37	29	31	30	4	13	4	5	3
Median time to first response, months	1.4	1.0	1.1	1.0	1.4	4.2	3.5	3.3	3.4	4.9
Median duration of response, months	19.9	18.5	16.3	16.9	22.4	13.1	10.8	13.1	12.9	20.5
Median TTP, months	24.0*	19.8	24.0	19.9	NE	16.6*	14.5	16.1	16.1	18.0
Median OS, months	NE*	28.7	NE	NE	NE	NE*	24.7	NE	31.9	NE
1-yr OS rate, %	88.6*	78.9	85.2	84.1	90.7	81.7*	71.8	77.4	76.7	84.2
2-yr OS rate, %	77.8*	65.5	70.9	70.1	81.4	68.2*	64.6	59.8	60.1	72.4
3-yr OS rate, %	71.6*	NE	68.2	60.7	76.9	58.7*	NE	42.2	41.5	67.9

Abbreviation: TTP, time to progression; OS, overall survival; VMP, bortezomib plus melphalan and prednisone; MP, melphalan and prednisone; GFR, glomerular filtration rate; CR, complete response.
*ITT population, n = 344 for VMP, n = 338 for MP.

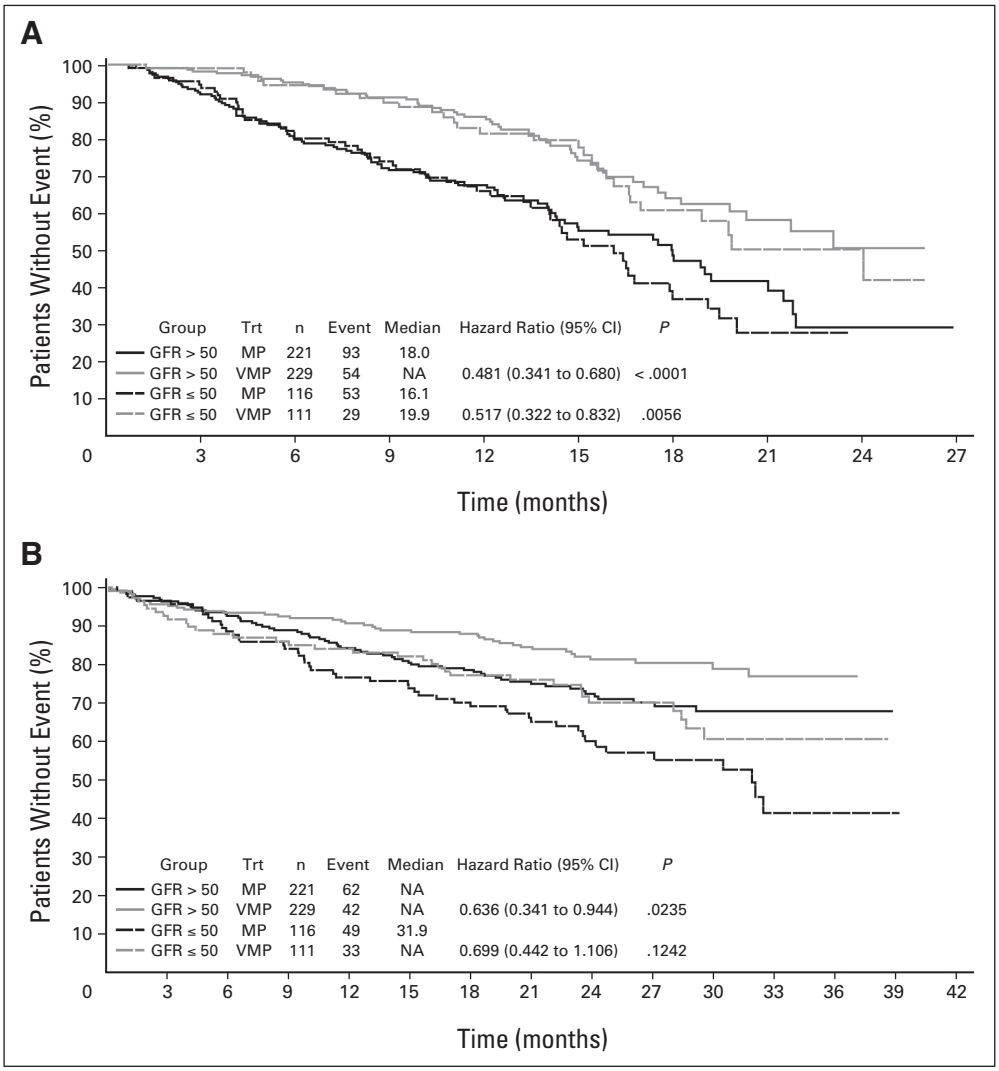

Fig 1. (A) Time to progression and (B) overall survival in the bortezomib plus melphalan and prednisone (VMP) and melphalan and prednisone (MP) arms in patients with normal renal function (glomerular filtration rate [GFR] > 50 mL/min) or renal impairment (GFR ≤ 50 mL/min). Trt, treatment; NA, not available.

reversal; with MP, respective rates were one (7%) of 15 and 39 (39%) of 101. Based on the renal response criteria of Ludwig et al[21] 44% (49 of 111) and 34% (40 of 116) of patients on the VMP and MP arms had CR^{renal}, one of two patients receiving MP had PR^{renal}, and eight (42%) of 19 and 10 (67%) of 15 patients on the VMP and MP arms had MR^{renal}. The majority of patients experiencing renal impairment reversal with both VMP (42 of 49; 86%) and MP (25 of 40; 63%) had GFR increases of ≥ 20 mL/min. An additional four VMP and nine MP patients had GFR increases of ≥ 20 mL/min without meeting the definition of renal impairment reversal.

Time to renal impairment reversal in patients with baseline GFR less than 50 mL/min was significantly shorter with VMP versus MP (Fig 2A). Among patients achieving renal impairment reversal, median time to reversal was 2.1 months (range, 0.2 to 11.8) with VMP and 2.4 months (range, 0.2 to 13.6) with MP.

Factors affecting rate of renal impairment reversal by univariate and multivariate analyses are presented in Table 3. By multivariate analysis, rate of reversal was significantly higher in patients age younger than 75 versus ≥ 75 years (OR, 0.45; $P = .006$) and in patients with less severe renal impairment (GFR ≥ 30 to < 50 *v* < 30 mL/min; OR, 0.43, $P = .027$). In addition, treatment with VMP versus MP approached statistical significance (OR, 1.50; $P = .07$). Response rate appeared higher in patients with reversible versus irreversible renal impairment with both VMP (36 [73%] of 49 *v* 40 [65%] of 62) and MP (24 [60%] of 40 *v* 28 [38%] of 74). Notably, 37% and 24% ($P = .1321$; one-sided, Fisher's exact test) of patients with GFR lower than 50 mL/min who did not respond to VMP and MP, respectively, experienced renal impairment reversal. In both arms, OS was not significantly different between patients who did or did not experience renal impairment reversal (Fig 2B).

Safety

Patients on the VMP arm with GFR ≤ 30, 31 to 50, and higher than 50 mL/min received a median of 9, 7, and 8 treatment cycles, respectively; in the MP arm, patients received a median of 4, 8, and 7 cycles, respectively. Safety profiles of VMP and MP overall and by renal cohort are presented in Table 4.[29] In both arms, among patients with GFR ≤ 50 mL/min rates of AEs of grade 4 and 5 maximum severity and serious AEs (SAEs) appeared somewhat higher compared with patients with GFR higher than 50 mL/min. Rates of discontinuations and bortezomib dose reductions due to AEs appeared similar between these cohorts in the VMP arm, while with MP the rate of

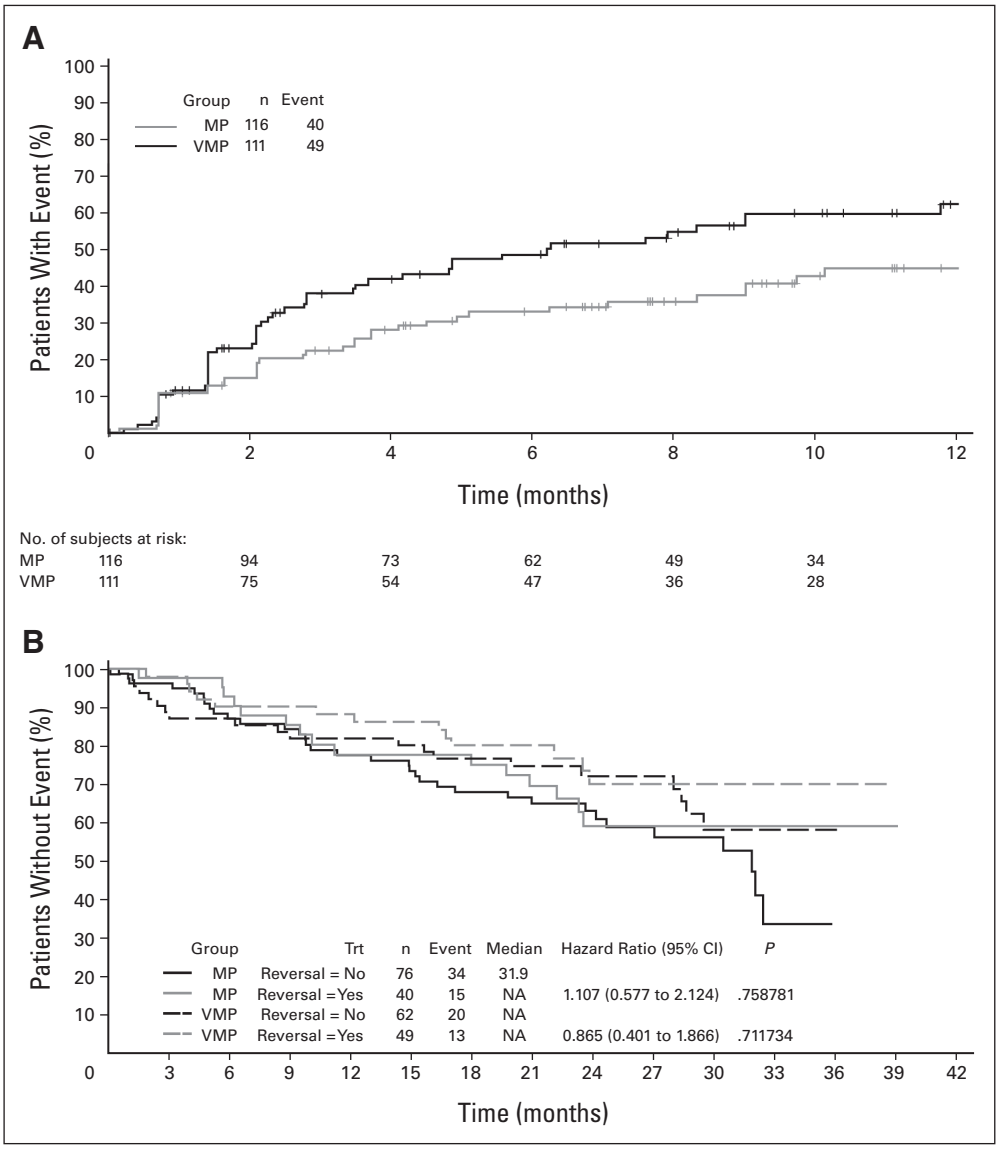

Fig 2. Kaplan-Meier analyses of (A) time to reversal of renal impairment with bortezomib plus melphalan and prednisone (VMP) and melphalan and prednisone (MP) in patients with baseline glomerular filtration rate less than 50 mL/min (50% quantile: 9.0 *v* 13.6 months; hazard ratio, 1.586, $P = .03$; 1-month rates: 13.2% and 9.6%, respectively), and (B) overall survival by reversal of renal impairment. Trt, treatment; NA, not available.

discontinuations due to AEs appeared slightly higher in patients with renal impairment. In both arms, there was a trend toward increasing numbers of melphalan dose reductions due to AEs with increasing renal impairment.

In the small cohort of patients with GFR ≤ 30 mL/min treated with VMP, hematologic toxicities were more common and overall rates of grade 4 AEs (42%) and SAEs (63%) appeared somewhat higher compared with patients with GFR 31 to 50 mL/min; however, rates of grade 5 AEs and discontinuations/bortezomib dose reductions due to AEs appeared similar/lower. The rate of renal and urinary disorders (including AEs of renal impairment/failure and azotemia) was higher in this cohort with severe impairment (32%) compared with patients with GFR 31 to 50 or higher than 50 mL/min (24% and 11%, respectively). With MP, rates of neutropenia, thrombocytopenia, grade 4 and 5 AEs, and discontinuations due to AEs appeared higher among patients with severe versus moderate impairment.

Patients achieving renal impairment reversal had a better safety profile than those with irreversible impairment; with VMP, rates of grade 5 AEs (8% *v* 15%), SAEs (43% *v* 60%), and discontinuations due to AEs (6% *v* 24%) appeared lower in patients with reversible impairment, while with MP, rates of grade 4 (25% *v* 37%) and grade 5 (10% *v* 13%) AEs, and discontinuations due to AEs (8% *v* 24%) also appeared lower among patients with reversible impairment.

DISCUSSION

This cohort analysis of the VISTA study is the largest analysis to date to assess the activity, tolerability, and impact of renal impairment reversal of treatment with a bortezomib-based regimen in patients with MM with renal impairment; it should be noted that due to the exclusion of patients with SCr higher than 2 mg/dL, patients in this analysis generally had moderate impairment. The results demonstrate that VMP is highly active and well tolerated in this population of previously untreated patients with renal impairment. Our findings reflect the overall efficacy results of VISTA,[25] with VMP remaining superior to MP across all renal cohorts in

Table 3. Factors* Affecting Rate of Reversal of Renal Impairment in the VMP and MP Arms and Overall, by Univariate and Multivariate Analysis

Factor	VMP Arm			MP Arm			Overall			
	Reversal Rate, %	OR (95% CI)	*P* (uni)	Reversal Rate, %	OR (95% CI)	*P* (uni)	Reversal Rate, %	OR (95% CI)	*P* (uni)	*P* (multi)
Age, years										
< 75	61	0.28 (0.13, 0.61)	.001	39	0.70 (0.32, 1.51)	.360	49	0.45 (0.26, 0.78)	.004	.006
≥ 75	30			31			30			
GFR mL/min										
≥ 30	46	0.69 (0.25, 1.92)	.483	39	0.11 (0.01, 0.90)	.039	42	0.43 (0.18, 0.99)	.047	.027
< 30	37			7			24			
Arm										
MP	—	—	—	34	—	—	34	1.50 (0.88, 2.57)	.137	.070
VMP	44			—			44			
Response by EBMT (≥ PR)†										
No	37	1.52 (0.67, 3.46)	.315	24	2.69 (1.21, 5.96)	.015	29	2.17 (1.24, 3.81)	.007	—
Yes	47			46			47			
Best M-protein response†										
< 50% reduction	26	2.57 (0.85, 7.71)	.093	17	3.67 (1.37, 9.82)	.010	20	3.31 (1.60, 6.85)	.001	—
≥ 50% reduction	48			42			45			

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; OR, odds ratio; PR, partial response; P (multi), *P* value by multivariate analysis; P (uni), *P* value by univariate analysis; ULN, upper limit of normal.

*Other factors analyzed–light-chain only MM versus other MM subtypes, calcium < ULN versus ≥ ULN, and Bence-Jones protein < 1g/day versus ≥ 1g/day–did not approach statistical significance in either arm by univariate analysis, and are not shown here.

†Factor not included in multivariate analysis due to being heavily influenced by treatment assignment.

terms of response rates, time to response, duration of response, TTP, and OS. While numerical differences were seen for all efficacy variables across all cohorts, differences between VMP and MP did not reach statistical significance for the small cohorts with severe renal impairment, likely due to limited patient numbers, although the ORs for response rates and HRs for TTP were consistent with other cohorts in favor of VMP. Similarly, while OS rates were higher, and HRs were consistently in favor of VMP versus MP and similar to the HR in the overall study population (0.644; $P = .0032$),[30] OS differences did not reach statistical significance

Table 4. Safety Profile, Including Rates of Key AEs, in the VMP and MP Arms and by Renal Cohort

AE, n (%)	VMP Arm					MP Arm				
		Renal Cohort, GFR, mL/min					Renal Cohort, GFR, mL/min			
	Total (N = 340)	≤ 30 (N = 19)	31-50 (N = 92)	≤ 50 (N = 111)	> 50 (N = 229)	Total (N = 337)	≤ 30 (N = 15)	31-50 (N = 101)	≤ 50 (N = 116)	> 50 (N = 221)
Any AE	338 (99)	19 (100)	91 (99)	110 (99)	228 (100)	326 (97)	15 (100)	98 (97)	113 (97)	213 (96)
Maximum severity of any AE:										
Grade 3	181 (53)	8 (42)	38 (41)	46 (41)	135 (59)	148 (44)	3 (20)	43 (43)	46 (40)	102 (46)
Grade 4	96 (28)	8 (42)	33 (36)	41 (37)	55 (24)	92 (27)	7 (47)	31 (31)	38 (33)	54 (24)
Grade 5	27 (8)	2 (11)	11 (12)	13 (12)	14 (6)	27 (8)	3 (20)	11 (11)	14 (12)	13 (6)
Key grade ≥ 3 AEs*										
Neutropenia	137 (40)	9 (47)	36 (39)	45 (41)	92 (40)	128 (38)	10 (67)	38 (38)	48 (41)	80 (36)
Thrombocytopenia	127 (37)	13 (68)	40 (43)	53 (48)	74 (32)	102 (30)	8 (53)	36 (36)	44 (38)	58 (26)
Anemia	62 (18)	8 (42)	18 (20)	26 (23)	36 (16)	92 (27)	5 (33)	37 (37)	42 (36)	50 (23)
Peripheral sensory neuropathy	44 (13)	3 (16)	8 (9)	11 (10)	33 (14)	—	—	—	—	—
Neuralgia	30 (9)	—	6 (7)	6 (5)	24 (10)	1 (< 1)	—	—	—	1 (< 1)
Pneumonia	29 (9)	1 (5)	7 (8)	8 (7)	21 (9)	22 (7)	—	9 (9)	9 (8)	13 (6)
Any SAE	155 (46)	12 (63)	46 (50)	58 (52)	97 (42)	121 (36)	6 (40)	41 (41)	47 (41)	74 (33)
Discontinuation due to AE	50 (15)	2 (11)	16 (17)	18 (16)	32 (14)	47 (14)	4 (27)	17 (17)	21 (18)	26 (12)
Dose reduction due to AE*:										
Bortezomib	165 (49)	7 (37)	48 (52)	55 (50)	110 (48)	—	—	—	—	—
2nd bortezomib reduction	62 (18)	3 (16)	15 (16)	18 (16)	44 (19)	—	—	—	—	—
Melphalan	50 (15)	5 (26)	21 (23)	26 (23)	24 (10)	44 (13)	4 (27)	16 (16)	20 (17)	24 (11)

*Bortezomib dose reductions (1.3→1.0→0.7 mg/m^2) were required if 3/8 (cycles 1-4) or 2/4 (cycles 5-9) doses in the previous cycle were skipped due to hematologic toxicity (platelets < 30 × 10^9/L, hemoglobin < 8 g/dL, absolute neutrophil count < 0.75 × 10^9/L). Melphalan dose reductions (9.0→6.75→4.5 mg/m^2) were required for grade 4 neutropenia or thrombocytopenia with platelets < 25 × 10^9/L (≥ 5 days). Bortezomib and melphalan dose reductions were required for grade ≥ 3 non-hematologic toxicities; bortezomib-associated peripheral neuropathy was managed according to established guidelines.[29]

among patients with renal impairment, possibly due to limited cohort size and limited numbers of deaths at data cutoff. Subsequent therapies may confound OS analyses; notably, 24% of renally impaired patients receiving MP and 25% with normal renal function received subsequent bortezomib-based therapy.

With VMP, overall response and CR rates, and TTP did not appear affected in patients with renal impairment (GFR $\leq$ 50 mL/min) compared with those with normal renal function (GFR $>$ 50 mL/min). Rapid responses were seen with VMP regardless of renal function, which is an important aspect of therapy for renally impaired patients.[31,32] In patients with renal impairment, notably severe impairment, OS rates appeared somewhat lower compared with patients with GFR higher than 50 mL/min; this may reflect the coexistence of a number of adverse factors, including more advanced disease in these patients. Our findings reflect other analyses demonstrating no impact of renal impairment on the activity of bortezomib-based therapy,[16,17,19,23,33] and support the findings of other studies showing substantial activity of bortezomib-based therapies in first-line and relapsed/refractory patients with MM with renal impairment, including those requiring dialysis.[15-23,33-36]

The safety profile of VMP appeared only somewhat affected by renal impairment, with rates of grade 4 and 5 AEs and SAEs appearing elevated but treatment duration and rates of discontinuations/bortezomib dose reductions due to AEs appearing similar between patients with renal impairment and normal renal function. Notably, the rate of grade $\geq$ 3 bortezomib-associated peripheral sensory neuropathy did not appear to differ between renal cohorts in the VMP arm. This reflects other studies in which renal impairment was not associated with substantial changes in the safety profile of bortezomib.[16,17,19,23] In the MP arm, similar trends were seen toward a somewhat elevated safety profile in patients with renal impairment, notably in the small cohorts with severe renal impairment; our findings thus suggest an effect independent of the addition of bortezomib, possibly associated with the previously reported increase in hematologic toxicities with MP in patients with moderate-to-severe renal impairment.[10] Melphalan may therefore not be the ideal partner for combination with bortezomib in patients with severe renal impairment; bortezomib and dexamethasone, bortezomib, doxorubicin, and dexamethasone, or bortezomib, cyclophosphamide, and dexamethasone may represent more suitable combinations, although data are not currently available for transplant-ineligible first-line patients with renal impairment.

VMP treatment resulted in a substantial rate (44%) of renal impairment reversal, with a trend toward significance compared with MP treatment on multivariate analysis; notably, the rates of renal impairment reversal were 37% and 7% with VMP and MP in patients with GFR less than 30 mL/min at baseline. Renal impairment reversal was rapid in some patients, likely associated with rapid responses to treatment, especially with VMP, although supportive measures such as hydration may also have been important. Other smaller studies of bortezomib-based regimens have also reported similar notable levels of renal impairment reversal, as well as elimination of dialysis-dependence in some patients.[15,18,20-22,33,35,36] Interestingly, some patients experienced reversal without meeting European Group for Blood and Marrow Transplantation criteria for response, a finding that has also been reported elsewhere,[3,22] suggesting that in some patients even minor reductions in tumor burden may be associated with reversal of primarily milder renal impairment. Furthermore, bortezomib has been shown to significantly reduce levels of cystatin-C, an endogenous marker for renal impairment,[37] in patients with relapsed MM.[38]

In our analysis, patients achieving renal impairment reversal demonstrated an improved safety profile versus those with irreversible impairment, possibly from reducing rates of melphalan-associated hematologic toxicities.[10] However, no OS advantage has to date been seen, possibly due to the limited prognostic importance of the generally moderate (GFR, 31 to $<$ 50 mL/min) renal impairment in these patients. Prolonged follow-up may be required for survival differences to emerge, while OS data may be confounded by the availability of other effective treatment options for patients with moderate renal impairment.

In conclusion, VMP is a feasible, active, and well-tolerated treatment option for newly diagnosed patients with MM with moderate renal impairment who are ineligible for high-dose therapy. VMP remained superior to MP regardless of renal function, and efficacy and safety of VMP were not substantially affected by the presence of moderate renal function impairment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: William Deraedt, Johnson & Johnson (C); Kevin Liu, Johnson & Johnson (C); Andrew Cakana, Johnson & Johnson (C); Helgi van de Velde, Johnson & Johnson (C) **Consultant or Advisory Role:** Meletios A. Dimopoulos, Millennium Pharmaceuticals (C), Ortho-Biotech (C); Paul G. Richardson, Millennium Pharmaceuticals (C), Johnson & Johnson (C), Celgene (C); Ofer Shpilberg, Johnson & Johnson (C); Martin Kropff, Janssen-Cilag (C), Celgene (C); Michel Delforge, Ortho-Biotech (C), Celgene (C); Rik Schots, Janssen-Cilag (C), Celgene (C); Jesús F. San Miguel, Janssen-Cilag (C), Celgene (C), Millennium Pharmaceuticals (C) **Stock Ownership:** William Deraedt, Johnson & Johnson; Kevin Liu, Johnson & Johnson, The Medicine Company; Helgi van de Velde, Johnson & Johnson **Honoraria:** Meletios A. Dimopoulos, Millennium Pharmaceuticals, Ortho-Biotech; Paul G. Richardson, Millennium Pharmaceuticals, Johnson & Johnson, Celgene; Martin Kropff, Janssen-Cilag, Celgene; Maria T. Petrucci, Janssen-Cilag, Celgene, Roche; Michel Delforge, Ortho-Biotech, Celgene; Rik Schots, Celgene; Maria-Victoria Mateos, Janssen-Cilag, Ortho-Biotech; Jesús F. San Miguel, Janssen-Cilag, Celgene, Millennium **Research Funding:** Meletios A. Dimopoulos, Ortho-Biotech; Nuriet K. Khuageva, Janssen Pharmaceutica NV; Julia Alexeeva, Janssen Pharmaceutica NV **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Meletios A. Dimopoulos, Paul G. Richardson, Martin Kropff, Helgi van de Velde, Jesús F. San Miguel
Provision of study materials or patients: Paul G. Richardson, Rudolf Schlag, Nuriet K. Khuageva, Ofer Shpilberg, Efstathios Kastritis, Martin

Kropff, Maria T. Petrucci, Michel Delforge, Julia Alexeeva, Rik Schots, Maria-Victoria Mateos, Andrew Cakana, Jesús F. San Miguel
Collection and assembly of data: Paul G. Richardson, Ofer Shpilberg, Efstathios Kastritis, Martin Kropff, Tamás Masszi, William Deraedt, Andrew Cakana, Helgi van de Velde
Data analysis and interpretation: Meletios A. Dimopoulos, Paul G. Richardson, William Deraedt, Kevin Liu, Andrew Cakana, Helgi van de Velde, Jesús F. San Miguel
Manuscript writing: Meletios A. Dimopoulos, Paul G. Richardson, Helgi van de Velde, Jesús F. San Miguel
Final approval of manuscript: Meletios A. Dimopoulos, Paul G. Richardson, Rudolf Schlag, Nuriet K. Khuageva, Ofer Shpilberg, Efstathios Kastritis, Martin Kropff, Maria T. Petrucci, Michel Delforge, Julia Alexeeva, Rik Schots, Tamás Masszi, Maria-Victoria Mateos, William Deraedt, Kevin Liu, Andrew Cakana, Helgi van de Velde, Jesús F. San Miguel

REFERENCES

1. Knudsen LM, Hippe E, Hjorth M, et al: Renal function in newly diagnosed multiple myeloma–a demographic study of 1353 patients: The Nordic Myeloma Study Group. Eur J Haematol 53:207-212, 1994

2. Dimopoulos MA, Kastritis E, Rosinol L, et al: Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia 22:1485-1493, 2008

3. Knudsen LM, Hjorth M, Hippe E: Renal failure in multiple myeloma: Reversibility and impact on the prognosis—Nordic Myeloma Study Group. Eur J Haematol 65:175-181, 2000

4. Alexanian R, Barlogie B, Dixon D: Renal failure in multiple myeloma: Pathogenesis and prognostic implications. Arch Intern Med 150:1693-1695, 1990

5. Bladé J, Fernandez-Llama P, Bosch F, et al: Renal failure in multiple myeloma: Presenting features and predictors of outcome in 94 patients from a single institution. Arch Intern Med 158:1889-1893, 1998

6. Eleutherakis-Papaiakovou V, Bamias A, Gika D, et al: Renal failure in multiple myeloma: Incidence, correlations, and prognostic significance. Leuk Lymphoma 48:337-341, 2007

7. Kyle RA, Gertz MA, Witzig TE, et al: Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78:21-33, 2003

8. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41, 1976

9. Abbott KC, Agodoa LY: Multiple myeloma and light chain-associated nephropathy at end-stage renal disease in the United States: Patient characteristics and survival. Clin Nephrol 56:207-210, 2001

10. Carlson K, Hjorth M, Knudsen LM: Toxicity in standard melphalan-prednisone therapy among myeloma patients with renal failure: A retrospective analysis and recommendations for dose adjustment. Br J Haematol 128:631-635, 2005

11. Chen N, Lau H, Kong L, et al: Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. J Clin Pharmacol 47:1466-1475, 2007

12. Greipp PR, San Miguel J, Durie BG, et al: International staging system for multiple myeloma. J Clin Oncol 23:3412-3420, 2005

13. Kastritis E, Anagnostopoulos A, Roussou M, et al: Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica 92:546-549, 2007

14. Sakhuja V, Jha V, Varma S, et al: Renal involvement in multiple myeloma: A 10-year study. Ren Fail 22:465-477, 2000

15. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al: Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: Identification of predictive factors. Clin Lymphoma Myeloma 9:302-306, 2009

16. Ailawadhi S, Mashtare TL, Coignet MV, et al: Renal dysfunction does not affect clinical response in multiple myeloma (MM) patients treated with bortezomib-based regimens. Blood 110:442a, 2007 (suppl; abstr 1477)

17. Bladé J, Sonneveld P, San Miguel JF, et al: Pegylated liposomal doxorubicin plus bortezomib in relapsed or refractory multiple myeloma: Efficacy and safety in patients with renal function impairment. Clin Lymphoma Myeloma 8:352-355, 2008

18. Chanan-Khan AA, Kaufman JL, Mehta J, et al: Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: A multicenter retrospective study. Blood 109:2604-2606, 2007

19. Jagannath S, Barlogie B, Berenson JR, et al: Bortezomib in recurrent and/or refractory multiple myeloma: Initial clinical experience in patients with impaired renal function. Cancer 103:1195-1200, 2005

20. Ludwig H, Drach J, Graf H, et al: Reversal of acute renal failure by bortezomib-based chemotherapy in patients with multiple myeloma. Haematologica 92:1411-1414, 2007

21. Ludwig H, Adam Z, Hajek R, et al: Bortezomib-doxorubicin-dexamethasone (BDD) for reversal of acute light chain induced renal failure (ARF) in multiple myeloma (MM): Results from a phase II study. Blood 112:1261a, 2008 (suppl; abstr 3682)

22. Roussou M, Kastritis E, Migkou M, et al: Treatment of patients with multiple myeloma complicated by renal failure with bortezomib-based regimens. Leuk Lymphoma 49:890-895, 2008

23. San-Miguel JF, Richardson PG, Sonneveld P, et al: Efficacy and safety of bortezomib in patients with renal impairment: Results from the APEX phase 3 study. Leukemia 22:842-849, 2008

24. Millennium Pharmaceuticals Inc: VELCADE® (bortezomib) for Injection: Prescribing information. Cambridge, MA; Issued June 2008, Rev 9, 2008

25. 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

26. 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

27. Bauer C, Melamed ML, Hostetter TH: Staging of chronic kidney disease: Time for a course correction. J Am Soc Nephrol 19:844-846, 2008

28. Levey AS, Coresh J, Balk E, et al: National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Ann Intern Med 139:137-147, 2003

29. Richardson PG, Briemberg H, Jagannath S, et al: Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol 24:3113-3120, 2006

30. San Miguel JF, Schlag R, Khuageva NK, et al: Updated follow-up and results of subsequent therapy in the phase III VISTA trial: Bortezomib plus melphalan-prednisone versus melphalan-prednisone in newly diagnosed multiple myeloma. Blood 112: 242A, 2008 (suppl; abstr 650)

31. Durie BG, Kyle RA, Belch A, et al: Myeloma management guidelines: A consensus report from the Scientific Advisors of the International Myeloma Foundation. Hematol J 4:379-398, 2003

32. Kyle RA, Rajkumar SV: Multiple myeloma. N Engl J Med 351:1860-1873, 2004

33. Gentile M, Ciolli S, Petrucci MT, et al: Bortezomib (VEL) based regimens in multiple myeloma (MM) patients with renal impairment (RI): A preliminary retrospective Italian multicenter study. Blood 112:1260a-1261a, 2008 (suppl; abstr 3681)

34. Gladney SP, Lonial S, Kaufman JL: Multiple myeloma presenting with advanced renal failure: A case report and new treatment options. Clin Lymphoma Myeloma 8:52-54, 2008

35. Malani AK, Gupta V, Rangineni R: Bortezomib and dexamethasone in previously untreated multiple myeloma associated with renal failure and reversal of renal failure. Acta Haematol 116:255-258, 2006

36. Mohrbacher A, Levine AM: Reversal of advanced renal dysfunction on bortezomib treatment in multiple myeloma patients. J Clin Oncol 23:612s, 2005 (suppl; abstr)

37. Hojs R, Bevc S, Ekart R, et al: Serum cystatin C as an endogenous marker of renal function in patients with mild to moderate impairment of kidney function. Nephrol Dial Transplant 21:1855-1862, 2006

38. Terpos E, Katodritou E, Tsiftsakis E, et al: Cystatin-C is an independent prognostic factor for survival in multiple myeloma and is reduced by bortezomib administration. Haematologica 94:372-379, 2009