

# Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/GMMG-HD4 Trial

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## ABSTRACT

### Purpose

We investigated whether bortezomib during induction and maintenance improves survival in newly diagnosed multiple myeloma (MM).

### Patients and Methods

In all, 827 eligible patients with newly diagnosed symptomatic MM were randomly assigned to receive induction therapy with vincristine, doxorubicin, and dexamethasone (VAD) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by high-dose melphalan and autologous stem-cell transplantation. Maintenance consisted of thalidomide 50 mg (VAD) once per day or bortezomib 1.3 mg/m<sup>2</sup> (PAD) once every 2 weeks for 2 years. The primary analysis was progression-free survival (PFS) adjusted for International Staging System (ISS) stage.

### Results

Complete response (CR), including near CR, was superior after PAD induction (15% v 31%;  $P < .001$ ) and bortezomib maintenance (34% v 49%;  $P < .001$ ). After a median follow-up of 41 months, PFS was superior in the PAD arm (median of 28 months v 35 months; hazard ratio [HR], 0.75; 95% CI, 0.62 to 0.90;  $P = .002$ ). In multivariate analysis, overall survival (OS) was better in the PAD arm (HR, 0.77; 95% CI, 0.60 to 1.00;  $P = .049$ ). In high-risk patients presenting with increased creatinine more than 2 mg/dL, bortezomib significantly improved PFS from a median of 13 months to 30 months (HR, 0.45; 95% CI, 0.26 to 0.78;  $P = .004$ ) and OS from a median of 21 months to 54 months (HR, 0.33; 95% CI, 0.16 to 0.65;  $P < .001$ ). A benefit was also observed in patients with deletion 17p13 (median PFS, 12 v 22 months; HR, 0.47; 95% CI, 0.26 to 0.86;  $P = .01$ ; median OS, 24 months v not reached at 54 months; HR, 0.36; 95% CI, 0.18 to 0.74;  $P = .003$ ).

### Conclusion

Bortezomib during induction and maintenance improves CR and achieves superior PFS and OS.

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## INTRODUCTION

High-dose melphalan (HDM) followed by autologous stem-cell transplantation (ASCT) is considered a standard of care for younger patients with multiple myeloma (MM).<sup>1-3</sup> In the setting of ASCT, high complete response (CR) rates have consistently resulted in prolonged progression-free survival (PFS) and overall survival (OS).<sup>4</sup> Chemotherapy with vincristine, doxorubicin, and dexamethasone (VAD) has been a standard induction in this setting.<sup>5,6</sup>

Proteasome inhibition (bortezomib) and immunomodulatory drugs (thalidomide, lenalidomide) have significant activity in patients with relapsed/refractory MM.<sup>7-10</sup> Bortezomib combined with melphalan and prednisone achieves 30% CR in newly diagnosed patients who are not eligible for transplantation.<sup>11</sup> Likewise, bortezomib combined with dexamethasone (VD) and thalidomide (VTD) results in an improvement of CR and in prolongation of PFS.<sup>12,13</sup> Although CR predicts for prolonged survival, these schedules have

not resulted in an improved OS.<sup>14,15</sup> In high-risk patients with MM presenting with renal failure or with deletion of chromosome 17p13 and/or t(4;14), survival remains poor.<sup>16-18</sup> Consolidation or maintenance therapy following high-dose therapy improves CR rate and PFS.<sup>19</sup> Maintenance with thalidomide prolongs PFS but not OS.<sup>20-22</sup> Lenalidomide maintenance improved PFS in one transplantation study and improved both PFS and OS in another.<sup>23,24</sup> Bortezomib has been studied as post-ASCT consolidation therapy.<sup>13,25,26</sup> Use of bortezomib as maintenance therapy has not yet been addressed in younger patients. We report on the results of an open-label randomized phase III trial that evaluated sustained bortezomib treatment during induction and maintenance.

## PATIENTS AND METHODS

### Eligibility

Patients 18 to 65 years of age with newly diagnosed MM Durie-Salmon stage II to III, WHO performance status 0 to 2, or WHO 3 when caused by MM, were eligible. Exclusion criteria were systemic amyloid light chain amyloidosis, nonsecretory MM, neuropathy grade  $\geq 2$ , active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma, HIV positivity, serum bilirubin  $\geq 30 \mu\text{mol/L}$  or aminotransferases  $\geq 2.5 \times$  normal level. Prior corticosteroids were allowed for a maximum of 5 days. Patients with renal impairment were not excluded. Local radiotherapy for painful MM lesions was allowed.

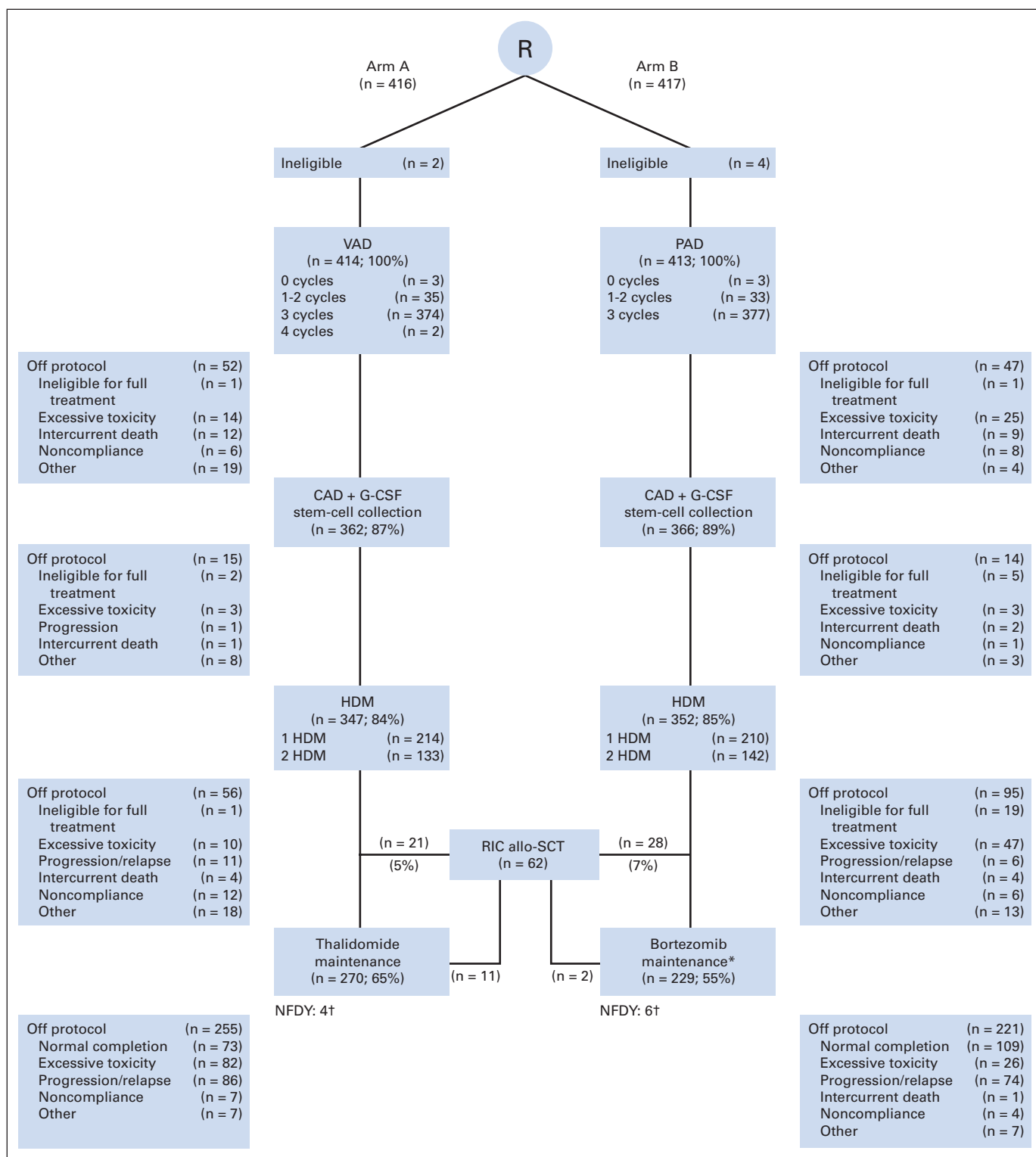
### Study Design

This investigator-sponsored, open-label, randomized phase III trial was designed and performed by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and the German Multicenter Myeloma Group (GMMG) by using one protocol, data management, and analysis. Patients were randomly assigned 1:1 to VAD induction,<sup>5</sup> followed by intensification with HDM and ASCT, followed by maintenance therapy with thalidomide (arm A) or bortezomib, doxorubicin, and dexamethasone (PAD),<sup>27</sup> followed by intensification with HDM and ASCT, followed by maintenance with bortezomib for 2 years (arm B). This design was chosen to evaluate sustained bortezomib treatment (64 administrations) as in VISTA.<sup>11</sup> Random assignments to VAD or PAD were balanced with use of a biased-coin minimization procedure, with the bias dependent on the average imbalance between numbers of patients already assigned to each treatment arm overall and within the stratification factors of the new patient.<sup>28</sup> The minimization was initially based on hospital, Durie-Salmon stage (2 v 3) and lactate dehydrogenase level ( $\leq$  upper limit of normal v greater than upper limit of normal). After the third amendment, the minimization was based on hospital and International Staging System (ISS) stage (I v II v III). Patients were randomly assigned via a Web-based application, Trial Online Process, and the assigned treatment arm was sent immediately via e-mail to local investigators. VAD was administered as three cycles of intravenous (IV) vincristine 0.4 mg per day on days 1 through 4, doxorubicin 9 mg/m<sup>2</sup> per day on days 1 through 4, and oral dexamethasone 40 mg per day on days 1 through 4, 9 to 12, and 17 to 20, every 28 days. PAD induction included three cycles of IV bortezomib 1.3 mg/m<sup>2</sup> per day on days 1, 4, 8, and 11; doxorubicin 9 mg/m<sup>2</sup> per day on days 1 through 4, and oral dexamethasone 40 mg per day on days 1 through 4, 9 to 12, and 17 to 20, every 28 days. Stem-cell collection was performed 4 to 6 weeks after induction.<sup>20</sup> HDM 200 mg/m<sup>2</sup> and ASCT were administered as described.<sup>20</sup> Per protocol, one or two cycles of HDM were planned, according to HOVON (single) and GMMG (double) standards, respectively. Patients randomly assigned to VAD received maintenance with thalidomide 50 mg per day for 2 years, starting at 4 weeks after HDM. Patients randomly assigned to PAD received maintenance with IV bortezomib 1.3 mg/m<sup>2</sup> once every 2 weeks for 2 years (n = 52) starting at 4 weeks after HDM. Patients with an HLA-identical sibling could proceed to nonmyeloablative allogeneic stem-cell transplantation (alloSCT) after HDM. Maintenance was not given after alloSCT. Supportive care was given as described in the Appendix (online only).

**Table 1.** Baseline Patient and Disease Characteristics

Characteristic	VAD (n = 414)		PAD (n = 413)	
	No.	%	No.	%
Study group				
HOVON	213	51	219	53
GMMG	201	49	194	47
Age, years				
Median	57		57	
Range	25-65		31-65	
Male sex	247	60	253	61
WHO performance stage				
0	183	44	193	47
1	173	42	170	41
2	47	11	31	8
3	8	2	15	4
Unknown	3	1	4	1
ISS stage				
I	144	35	144	35
II	124	30	150	36
III	107	26	81	20
Unknown	39	9	38	9
M-protein isotype				
IgA	97	23	92	22
IgG	234	57	251	61
IgD	3	1	5	1
LCD	78	19	63	15
Other	2	0	2	0
M-protein light chain				
Kappa	278	67	277	67
Lambda	136	33	135	33
Unknown	0	0	1	0
Creatinine, mg/dL				
$\leq 2$	368	89	376	91
$> 2$	45	11	36	9
Unknown	1	0	1	0
No. of skeletal lesions				
0	96	23	102	25
1-2	42	10	44	11
$\geq 3$	264	64	255	62
Unknown	12	3	12	3
Serum LDH				
$\leq$ ULN	331	80	329	80
$>$ ULN	72	17	72	17
Unknown	11	3	12	3
Genetic abnormalities				
del(13q)				
Done	372	90	361	88
Positive, % of done	164	44	148	41
t(4;14)				
Done	262	63	250	61
Positive, % of done	35	13	35	14
del(17p13)				
Done	313	76	289	70
Positive, % of done	40	13	25	9
Median $\beta_2$ -microglobulin, mg/L	3.40		3.40	
Median hemoglobin, mmol/L	6.7		6.6	
Median calcium, mmol/L	2.31		2.34	
Median No. of bone marrow plasma cells	45		40	

Abbreviations: GMMG, German Multicenter Myeloma Group; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Group; Ig, immunoglobulin; ISS, International Staging System; LCD, light-chain disease; LDH, serum lactate dehydrogenase; PAD, bortezomib, doxorubicin, dexamethasone; ULN, upper limit of normal; VAD, vincristine, doxorubicin, dexamethasone.



**Fig 1.** CONSORT diagram of 827 adult patients with multiple myeloma (MM) in the Dutch-Belgian Hemato-Oncology Group 65/German Multicenter Myeloma Group HD4 (HOVON-65/GMMG-HD4) study by treatment arm. allo-SCT, allogeneic stem-cell transplantation; CAD, cyclophosphamide, doxorubicin, dexamethasone; G-CSF, granulocyte colony-stimulating factor; HDM, high-dose melphalan; PAD, bortezomib, doxorubicin, and dexamethasone; R, random assignment; RIC, reduced intensity conditioning; VAD, vincristine, doxorubicin, and dexamethasone. (\*) Including one patient with thalidomide plus bortezomib and one patient with thalidomide only. (†) NFDY, no further data yet.

**Table 2.** Response After Induction, After High-Dose Melphalan, and Overall, According to Prognostic Factors

Response	VAD (n = 414)		PAD (n = 413)		P
	No.	%	No.	%	
Response after induction					
CR	7	2	29	7	< .001
≥ nCR	20	5	46	11	< .001
≥ VGPR	59	14	174	42	< .001
≥ PR	222	54	322	78	< .001
Response after HDM					
CR	37	9	85	21	< .001
≥ nCR	62	15	127	31	< .001
≥ VGPR	150	36	254	62	< .001
≥ PR	312	75	363	88	< .001
Response overall					
CR	99	24	147	36	< .001
≥ nCR	140	34	201	49	< .001
≥ VGPR	230	56	312	76	< .001
≥ PR	343	83	373	90	.002
Response upgrade during maintenance					
Any response upgrade	99	24	93	23	.64
< CR→CR	45	11	48	12	.73
< nCR→nCR	16	4	23	6	.25
< VGPR→VGPR	27	7	20	5	.30
< PR→PR	11	3	2	0	.008
ISS stage I	(n = 144)		(n = 144)		
CR	37	26	59	41	.006
≥ nCR	58	40	78	54	.018
≥ VGPR	94	65	115	80	.005
≥ PR	130	90	132	92	.68
ISS stage II	(n = 124)		(n = 150)		
CR	29	23	51	34	.05
≥ nCR	35	28	70	47	.002
≥ VGPR	59	48	109	73	< .001
≥ PR	100	81	134	89	.04
ISS stage III	(n = 107)		(n = 81)		
CR	24	22	26	32	.14
≥ nCR	35	33	35	43	.14
≥ VGPR	57	53	56	69	.03
≥ PR	82	77	70	86	.09
ISS stage unknown	(n = 39)		(n = 38)		
CR	9	23	11	29	.56
≥ nCR	12	31	18	47	.13
≥ VGPR	20	51	32	84	.002
≥ PR	31	79	37	97	.01
β <sub>2</sub> -microglobulin > 3 mg/L	(n = 220)		(n = 223)		
CR	50	23	77	35	.006
≥ nCR	67	30	103	46	< .001
≥ VGPR	114	52	163	73	< .001
≥ PR	173	79	198	89	.004
Creatinine > 2 mg/dL	(n = 45)		(n = 36)		
CR	6	13	13	36	.02
≥ nCR	12	27	19	53	.02
≥ VGPR	18	40	28	78	< .001
≥ PR	29	64	31	86	.02
Genetic abnormalities					
del(13/13q14)	(n = 164)		(n = 148)		
≥ nCR	53	32	76	51	< .001
≥ VGPR	88	54	124	84	< .001
t(4;14)	(n = 35)		(n = 35)		
≥ nCR	11	31	20	57	.03
≥ VGPR	20	57	30	86	.007
del(17p13)	(n = 40)		(n = 25)		
≥ nCR	8	20	13	52	.008
≥ VGPR	17	43	18	72	.02

Abbreviations: CR, complete response; HDM, high-dose melphalan; ISS, International Staging System; nCR, near complete response; PAD, bortezomib, doxorubicin, dexamethasone; PR, partial response; VAD, vincristine, doxorubicin, dexamethasone; VGPR, very good partial response.

This study was approved by the ethics committees of the Erasmus University Medical Center, the University of Heidelberg, and the participating sites. All patients gave written informed consent, and the trial was conducted according to the European Clinical Trial Directive 2005 and the Declaration of Helsinki.

### Response Assessments and End Points

Clinical characteristics were recorded at diagnosis. Cytogenetic studies were performed as described in the Appendix.<sup>29</sup> Evaluation of response was performed according to modified European Group for Blood and Marrow Transplantation (EBMT) criteria.<sup>30</sup> Near CR (nCR) and very good partial response (VGPR) were implemented as in the International Myeloma Working Group (IMWG) response criteria.<sup>31</sup> nCR was defined as CR with positive or missing immunofixation,<sup>8</sup> and VGPR was defined as more than 90% reduction of serum M-protein and urine light chain less than 100 mg/24 hours. CR required negative serum/urine immunofixation and bone marrow morphology evaluation. Responses were assessed after induction, after first and second transplantation, at 2-month intervals during maintenance, and until progression. PFS was calculated from random assignment until progression, relapse, or death, whichever came first. Patients who received a nonmyeloablative alloSCT, however, were censored at the date of alloSCT. PFS without censoring of alloSCT patients has been denoted as PFS<sub>A</sub>. OS was measured from random assignment until death from any cause. Patients alive at the date of last contact were censored.

### Statistical Analysis

The primary objective of the study was to compare PFS between the treatment arms. The expected PFS in the VAD arm was 50% at 3 years. To detect a hazard ratio (HR) of 0.74 with a power of 80%, which corresponds to an increase of 3-year PFS from 50% to 60% (two-sided significance level of  $\alpha = .049$ , because of one planned interim analysis at a significance level of  $\alpha = .001$ ), and assuming 3 years of accrual, additional follow-up time of 2 years, and 10% alloSCT, 800 patients had to be randomly assigned and 356 events had to be observed. All analyses were performed by intention-to-treat, and the primary analysis was done with a multivariate Cox regression that included adjustment for ISS stage.

Secondary end points included response, PFS<sub>A</sub> (without censoring patients with alloSCT), PFS/PFS<sub>A</sub> from last HDM, OS, safety, and toxicity. The detailed statistical analysis is provided in the Appendix.

## RESULTS

### Patients

In all, 833 patients were recruited from May 2005 to May 2008. Two (VAD) and four (PAD) ineligible patients were excluded from

analyses because they had nonsecreting myeloma ( $n = 4$ ), misdiagnosis, or prior treatment ( $n = 2$ ). Thus, 827 patients were randomly assigned to VAD ( $n = 414$ ) or PAD ( $n = 413$ ). Patient characteristics at inclusion did not differ between the two groups (Table 1). Eighty-one patients (10%) with impaired renal function (Durie-Salmon stage B; serum creatinine more than 2 mg/dL) were included.

### Adherence to Treatment

The flow of patients through the protocol is shown in Figure 1. Intensification with first HDM was achieved in 84% of patients, and 69% of GMMG patients completed a second HDM. Of those patients in the VAD arm, 77 (22%) of 347 went off protocol after HDM because of alloSCT ( $n = 21$ ; 6%), persisting toxicity ( $n = 11$ ; 3%), or other reasons ( $n = 45$ ; 13%), although 270 patients (78%) started maintenance treatment. In the PAD arm, 123 (35%) of 352 patients went off protocol because of alloSCT ( $n = 28$ ; 8%), persisting toxicity ( $n = 47$ ; 13%, mainly polyneuropathy), or other ( $n = 48$ ; 14%), and 229 (65%) started maintenance with bortezomib ( $P = .004$ ; Fig 1). Persisting toxicity was an exclusion criterium for starting maintenance and, within the group of patients who went off protocol (excluding alloSCT patients), this was observed in 11 (14%) of 77 in the VAD arm versus 47 (38%) of 123 in the PAD arm ( $P < .001$ ). Normal completion of maintenance was achieved in 73 (27%) of 270 patients (VAD) and 109 (47%) of 229 patients (PAD; Appendix Table A1, online only).

### Response

Overall response is given in Table 2. The CR rate was 24% in patients who were randomly assigned to VAD and 36% in patients randomly assigned to PAD ( $P < .001$ ). Overall nCR plus CR rates were 34% versus 49%, respectively ( $P < .001$ ). After induction, all responses (ie, at least partial response [PR], at least VGPR, and at least nCR) were superior in the PAD arm. Response rates increased from induction to significantly higher than equal to or greater than VGPR and equal to or greater than nCR following HDM/ASCT in the PAD arm. The response rate for nCR plus CR after transplantation was 15% (VAD) versus 31% (PAD), respectively ( $P < .001$ ). During maintenance, an upgrade of response (from less than PR to PR, less than VGPR to VGPR, less than nCR to nCR, or less than CR to CR) was

**Table 3.** Multivariate Analysis of Risk Factors for PFS and OS

Risk Factor	PFS			OS		
	HR	95% CI	P	HR	95% CI	P
PAD treatment arm	0.74	0.62 to 0.89	.001	0.77	0.60 to 1.00	.049
Age (years)	1.00	0.99 to 1.02	.53	1.00	0.99 to 1.02	.61
Female sex	0.85	0.70 to 1.02	.08	0.85	0.65 to 1.11	.24
ISS stage (I, II, III)	1.24	1.09 to 1.41	.001	1.45	1.21 to 1.74	< .001
WHO PS (0, 1, 2, 3)	1.25	1.11 to 1.42	< .001	1.52	1.29 to 1.79	< .001
IgA*	1.59	1.19 to 2.13	.002	1.81	1.19 to 2.75	.006
IgG†	1.33	1.03 to 1.72	.03	1.54	1.07 to 2.23	.02
Durie-Salmon stage 3	1.02	0.79 to 1.33	.86	1.02	0.70 to 1.48	.93
LDH > ULN	1.28	1.01 to 1.63	.04	1.68	1.24 to 2.29	.001
del(13/13q14)	1.39	1.13 to 1.70	.002	1.70	1.29 to 2.23	< .001
SG (double HDM policy)	0.87	0.73 to 1.05	.15	0.75	0.57 to 0.97	.03

Abbreviations: HDM, high-dose melphalan; HR, hazard ratio; Ig, immunoglobulin; ISS, International Staging System; LDH, lactate dehydrogenase; OS, overall survival; PAD, bortezomib, doxorubicin, dexamethasone; PFS, progression-free survival; PS, performance status; SG, study group; ULN, upper limit of normal.

\*M-protein is IgA compared with no IgA (IgG, IgD, light-chain disease, and other).

†M-protein is IgG compared with no IgG (IgA, IgD, light-chain disease, and other).



observed in 24% of patients in the VAD arm and 23% in the PAD arm (Table 2). The median time to any response upgrade after start of maintenance was 6 months for VAD (range, 1 to 35 months) versus 7 months for PAD (range, 1 to 57 months).

### PFS and OS

The median PFS was 28 months for the VAD arm and 35 months for the PAD arm. Patients who were assigned to PAD had a significantly better PFS (HR, 0.75; 95% CI, 0.62 to 0.90;  $P = .002$ ) when adjusted for ISS (primary analysis) and also in the multivariate analysis (HR, 0.74; 95% CI, 0.62 to 0.89;  $P = .001$ ; Table 3, and Fig 2A). The median PFS<sub>A</sub> (ie, without censoring of alloSCT) was 28 months (VAD) versus 34 months (PAD), respectively (Fig 2B).

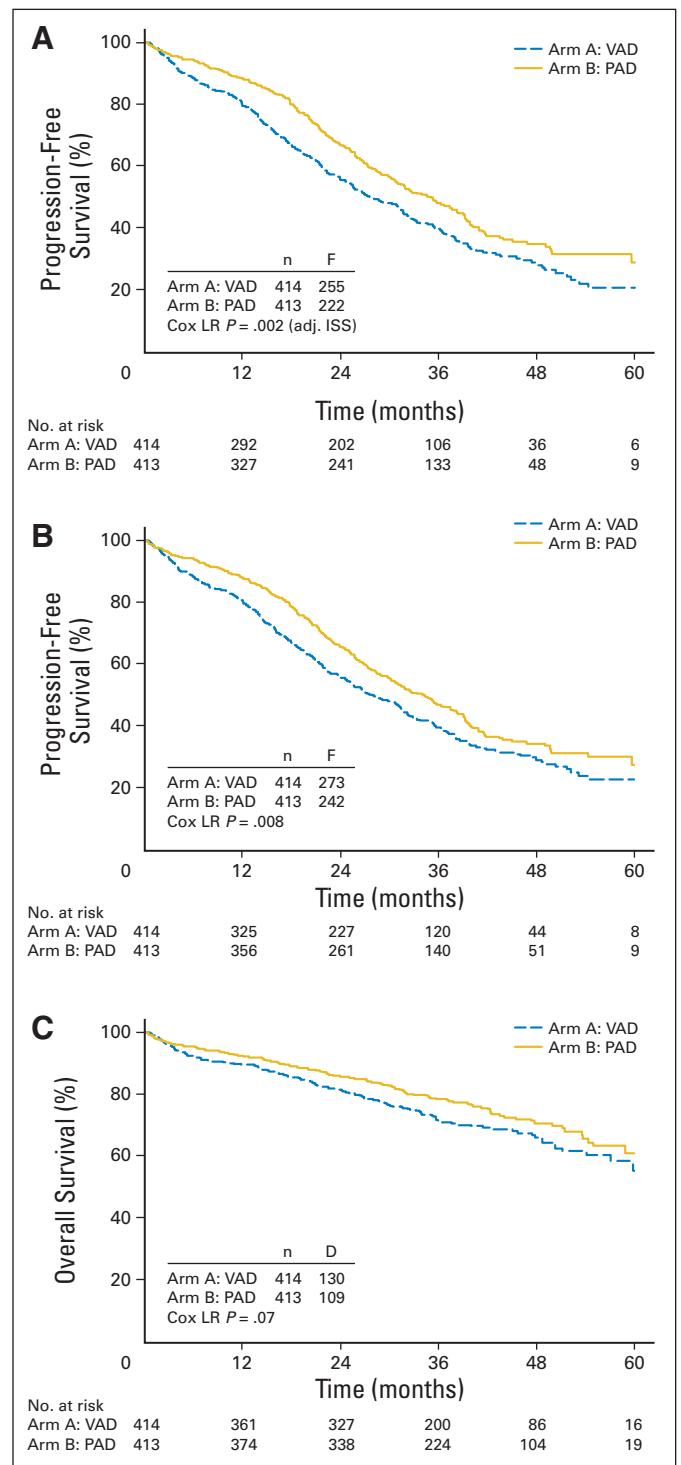
Median OS was not reached at 66 months in either arm, with 5-year OS of 55% (VAD) versus 61% (PAD; Fig 2C). When OS was adjusted for ISS, an HR of 0.81 (95% CI, 0.63 to 1.05;  $P = .11$ ) was noted, but OS difference reached statistical significance in the multivariate analysis (HR, 0.77; 95% CI, 0.60 to 1.00;  $P = .049$ ). It should be noted that both HRs and 95% CIs are quite similar. OS also differed between study groups, with the GMMG patients having a better OS (HR, 0.75; 95% CI, 0.57 to 0.97;  $P = .03$ ). An analysis of PFS calculated from the time of last HDM ( $n = 645$ ) showed a significant difference in favor of the PAD arm, with a median of 26 months versus 31 months (Appendix Fig A1A, online only). This indicates that although post-transplantation bortezomib and thalidomide both achieved response upgrades, bortezomib contributed more to improvement of PFS. In a landmark analysis starting at 12 months after random assignment for 585 patients (283, VAD; 302, PAD) who had received HDM/ASCT and were still without progression, PFS ( $P = .04$ ; Appendix Fig A1B) and OS ( $P = .05$ ; Appendix Fig A1C) were improved in the PAD arm.

### Safety

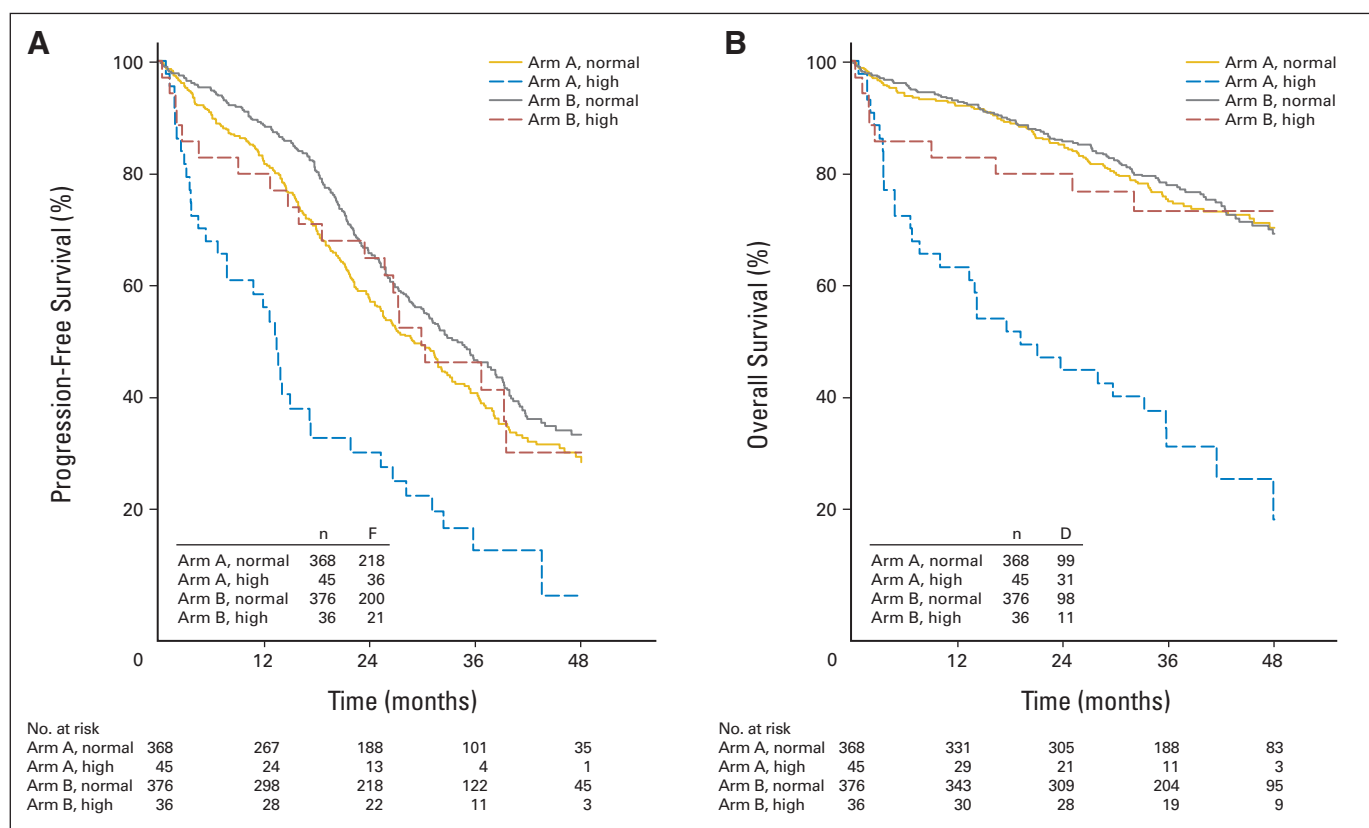
The safety profiles and most common toxicities are listed in Appendix Table A2 (online only). Peripheral neuropathy (PNP) occurred more often in the PAD arm. Within the first year of treatment, PNP grades 2 to 4 were reported in 18% (VAD) and 40% (PAD) of patients (HR, 1.50; 95% CI, 1.20 to 1.88;  $P < .001$ ). In addition, newly developed grade 3 to 4 PNP occurred in 8% of patients during thalidomide maintenance and 5% of patients during bortezomib maintenance. In 82 (30%) of 270 patients receiving thalidomide maintenance, toxicity was a reason to stop treatment prematurely compared with 26 (11%) of 229 patients receiving bortezomib maintenance ( $P < .001$ ). The most frequent toxicities occurring during maintenance are listed in Appendix Table A2. Progression or relapse were reasons to stop maintenance prematurely in 86 (32%) of 270 patients during thalidomide treatment versus 74 (32%) of 229 patients during bortezomib treatment.

### Secondary Analyses

To explore a possible differential effect of bortezomib treatment in any of the subgroups, the effect of treatment was estimated separately by HRs for PFS and OS, with associated 95% CIs combined with tests for interaction. The interactions were especially significant for serum creatinine, fluorescent in situ hybridization (FISH) del(13q14) and FISH del(17p13). Results of these subgroups are presented in detail in Neben et al.<sup>32</sup> Bortezomib resulted in a superior outcome in patients with increased serum creatinine. In these patients, both median PFS (13 v 30 months; HR, 0.45; 95% CI, 0.26 to 0.78;  $P = .004$ )



**Fig 2.** Kaplan-Meier survival curves among patients with multiple myeloma, according to randomly assigned treatment arm. (A) Progression-free survival (censored at allogeneic stem-cell transplantation); (B) progression-free survival (not censored at allogeneic stem-cell transplantation); (C) overall survival. adj. ISS, adjusted for International Staging System stage; Cox LR, Cox logistic regression; D, number of deaths; F, number of treatment failures (ie, progression, relapse, or death); PAD, bortezomib, doxorubicin, and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone.



**Fig 3.** Kaplan-Meier survival curves of progression-free survival and overall survival according to treatment arm within subgroups according to creatinine level at presentation. (A) Progression-free survival in patients with creatinine  $\leq 2$  mg/dL (VAD [vincristine, doxorubicin, and dexamethasone], gold; PAD [bortezomib, doxorubicin, and dexamethasone], gray) or more than 2 mg/dL (VAD, blue; PAD, red). (B) Overall survival in patients with creatinine  $\leq 2$  mg/dL (VAD, gold; PAD, gray) or more than 2 mg/dL (VAD, blue; PAD, red). D, number of deaths; F, number of treatment failures (ie, progression, relapse, or death).

and OS (21 v 54 months; HR, 0.33; 95% CI, 0.16 to 0.65;  $P < .001$ ) dramatically improved with bortezomib compared with VAD/thalidomide (Fig 3). In patients with normal serum creatinine, PFS (median 31 v 35 months; HR, 0.80; 95% CI, 0.66 to 0.97;  $P = .02$ ) remained superior in the PAD arm, but OS was similar between the arms (59% v 62% at 5 years; HR, 0.94; 95% CI, 0.71 to 1.25;  $P = .94$ ).

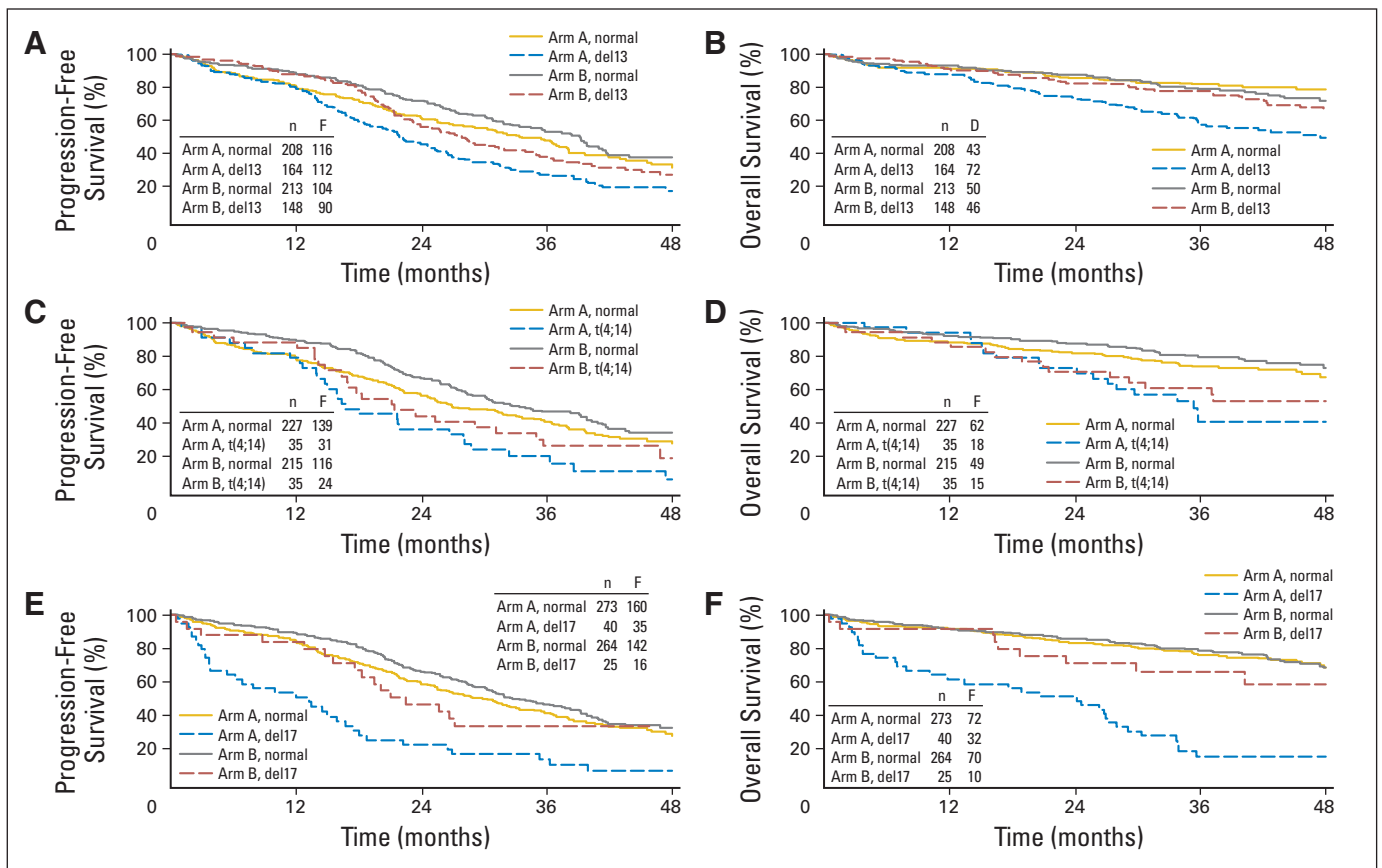
Subgroup analyses were also performed for FISH abnormalities, such as del(13q14), t(4;14), and del(17p13) (Table 1). In these analyses, patients with abnormal FISH results were compared with all patients without the abnormality. In patients with del(13q14), a negative impact on PFS was observed in both treatment arms (Fig 4A). OS in patients with this deletion was similar to the OS in patients with no del(13q14) in the PAD arm and significantly better than OS in the VAD arm (median OS, 49 v 59 months; HR, 0.60; 95% CI, 0.42 to 0.87;  $P = .007$ ; Fig 4B). t(4;14) was associated with worse PFS (HR, 1.76; 95% CI, 1.32 to 2.36;  $P < .001$ ) and OS (HR, 2.13; 95% CI, 1.45 to 3.15;  $P < .001$ ). Although PAD achieved better results in patients with t(4;14), this did not reach statistical significance (Figs 4C and 4D).

In patients with del(17p13), both PFS (median PFS, 12 v 22 months; HR, 0.47; 95% CI, 0.26 to 0.86;  $P = .01$ ; Fig 4E) and OS (median OS, 24 v 54 months; HR, 0.36; 95% CI, 0.18 to 0.74;  $P = .003$ ; Fig 4F) were significantly better in the PAD arm. In patients without del(17p13), OS was identical in both treatment arms (HR, 0.96; 95% CI, 0.69 to 1.34;  $P = .81$ ). An analysis of all FISH abnormalities has been published separately.<sup>32</sup>

Because the double HDM/ASCT policy was statistically significant in the multivariate analysis for OS, it was decided to also analyze some of the outcomes for HOVON (single HDM/ASCT) and GMMG (double HDM/ASCT). In the HOVON patients, the nCR/CR rate after maintenance was 29% in the VAD arm and 47% in the PAD arm (odds ratio, 2.21; 95% CI, 1.49 to 3.30;  $P < .001$ ). The median PFS was 24 months versus 32 months (HR, 0.70; 95% CI, 0.55 to 0.91;  $P = .006$ ). OS was 55% at 5 years in both arms (HR, 0.87; 95% CI, 0.62 to 1.20;  $P = .39$ ). In the GMMG patients, the nCR/CR rate after maintenance was 39% in the VAD arm and 51% in the PAD arm (odds ratio, 1.58; 95% CI, 1.06 to 2.35;  $P = .03$ ). The median PFS was 31 months versus 36 months (HR, 0.80; 95% CI, 0.62 to 1.04;  $P = .09$ ). OS was 54% versus 70% at 5 years (HR, 0.69; 95% CI, 0.46 to 1.04;  $P = .07$ ).

## DISCUSSION

This randomized multicenter trial in patients with MM who were eligible for high-dose therapy demonstrates that bortezomib during induction and maintenance treatment results in a better response, quality of response, PFS, and OS. In this trial, no random assignment for maintenance therapy was performed; consequently, this cannot be independently assessed. Instead, we attempted to determine whether bortezomib before and after high-dose therapy might result in prolonged PFS. Maintenance treatment with bortezomib for 2 years was



**Fig 4.** Kaplan-Meier survival curves of progression-free survival (PFS) and overall survival (OS) according to treatment arm within subgroups according to del(13/13q) or t(4;14) or according to del(17p). In all panels, patients without data regarding the specific abnormality have been excluded. (A) PFS in patients without del(13q) (VAD [vincristine, doxorubicin, and dexamethasone], gold; PAD [bortezomib, doxorubicin, and dexamethasone], gray) or with del(13q) (VAD, blue; PAD, red). (B) OS in patients without del(13q) (VAD, gold; PAD, gray) or with del(13q) (VAD, blue; PAD, red). (C) PFS in patients without t(4;14) (VAD, gold; PAD, gray) or with t(4;14) (VAD, blue; PAD, red). (D) OS in patients without t(4;14) (VAD, gold; PAD, gray) or with t(4;14) (VAD, blue; PAD, red). (E) PFS in patients without del(17p) (VAD, gold; PAD, gray) or with del(17p) (VAD, blue; PAD, red). (F) OS in patients without del(17p) (VAD, gold; PAD, gray) or with del(17p) (VAD, blue; PAD, red). D, number of deaths; F, number of treatment failures (ie, progression, relapse, or death).

much better tolerated than thalidomide maintenance, with fewer patients stopping their treatment prematurely. Bortezomib maintenance significantly improved the nCR plus CR rate from 31% to 49%. A landmark analysis indicated that nCR plus CR at 12 months was associated with better PFS and OS. The subgroup analyses show that the superior outcome with bortezomib is predominantly accomplished in patients with high-risk disease, myeloma-related renal failure, and del(17p). There seemed to be less difference in PFS between the treatment arms in patients without the high-risk characteristics. In addition, OS was better in the GMMG group, which performed standard double HDM with ASCT in 69% of patients in contrast to HOVON (single HDM). Previous trials have not clearly demonstrated a survival benefit of double versus single HDM.<sup>33,34</sup> Because the trial was not powered to compare single versus double HDM, the question remains open.

Other studies have explored induction treatment with bortezomib in two- or three-drug combinations such as bortezomib and dexamethasone (BD), BD with cyclophosphamide (VCD), BD with thalidomide (VTD), or BD with lenalidomide (VRD) in newly diagnosed patients. All observed a higher VGPR or CR rate and/or an improvement of PFS but not OS compared with standard treatment.<sup>13,35-38</sup> The Intergroupe Francophone du Myélome (IFM 2005-01) trial<sup>35</sup> was not

designed to evaluate OS. In the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and University of Arkansas for Medical Sciences (UAMS) TT2 and TT3 trials, there was no difference in OS.<sup>25,36</sup> In Total Therapy 3, bortezomib was given from induction through consolidation and maintenance, resulting in a 5-year OS of 72%.<sup>39</sup> Bortezomib consolidation after HDM was recently investigated.<sup>25</sup> Monotherapy of 20 injections over 21 weeks was well tolerated (mean total dose, 82%), the rate of VGPR or better increased from 39% to 70%, and median PFS increased from 20 months (VAD) to 27 months (PAD).

The Spanish PETHEMA group used VTD induction without consolidation, showing a post-ASCT CR rate of 46%.<sup>40</sup> In GIMEMA, VTD induction and consolidation after HDM resulted in an improved CR from 19% after induction to 42% after second HDM and 49% after consolidation.<sup>13</sup> These results indicate that post-HDM consolidation with bortezomib may increase CR or VGPR. Maintenance treatment with bortezomib, as in this trial, may offer the same CR/nCR and an improved PFS and OS.

Bortezomib-emergent peripheral neuropathy (BiPN) was the prevalent toxicity during induction, preventing a substantial number of patients from starting maintenance. In those who started maintenance, 5% experienced BiPN grade 3 to 4 toxicity. More



patients were unable to complete thalidomide maintenance treatment. Hence, the lower percentage of failures in the bortezomib arm may have contributed to the better PFS/OS in that group. Prolonged administration of bortezomib in the once every 2 weeks schedule seems feasible, and therefore it is important to prevent BiPN during induction, enabling patients to continue into maintenance. The tolerability of the two-weekly schedule is in line with the reported weekly schedule.<sup>4</sup> In addition, subcutaneous administration may further improve tolerability.<sup>41</sup> Recently, a significant prolongation of PFS and/or OS was demonstrated with lenalidomide maintenance after high-dose therapy.<sup>23,24</sup> Future trials will address the optimal choice for maintenance treatment.

Our subgroup analyses revealed that bortezomib was superior for CR/nCR, PFS, and OS in patients presenting with renal insufficiency, almost to the level of patients without organ failure. Although the safety and efficacy of bortezomib in renal failure has been observed in phase II studies,<sup>42-44</sup> this trial prospectively defines the benefit of bortezomib in these high-risk patients.

The reported better outcome with bortezomib of patients with t(4;14) was not confirmed. Although bortezomib treatment resulted in better PFS and OS, the outcome remained inferior compared with patients without t(4;14). Bortezomib significantly improved PFS and OS in patients with del(13q14) and more importantly in del(17p13), identifying a potential effective treatment option in this high-risk group. In the recent IFM trial<sup>17</sup> that used bortezomib plus dexamethasone for induction, no improvement of PFS was observed in patients with del(17p), indicating that induction with bortezomib may not be sufficient and that longer treatment may be required for better outcome. Because a plateau in PFS and OS was not observed, longer follow-up is warranted. In conclusion, bortezomib during induction and maintenance improves response, PFS, and OS in patients with MM.

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

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