JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bortezomib Plus Dexamethasone Is Superior to Vincristine Plus Doxorubicin Plus Dexamethasone As Induction Treatment Prior to Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: Results of the IFM 2005-01 Phase III Trial

Jean-Luc Harousseau, Michel Attal, Hervé Avet-Loiseau, Gerald Marit, Denis Caillot, Mohamad Mohty, Pascal Lenain, Cyrille Hulin, Thierry Facon, Philippe Casassus, Mauricette Michallet, Hervé Maisonneuve, Lotfi Benboubker, Frédéric Maloisel, Marie-Odile Petillon, Iain Webb, Claire Mathiot, and Philippe Moreau

See accompanying articles doi: 10.1200/JCO.2010.28.1238 and 10.1200/JCO.2010.28.3945

From the Centre René Gauducheau, Nantes/St. Herblain; Hôpital Purpan, Centre Hospitalier Universitaire Toulouse, Toulouse; Centre Hospitalier Universitaire Nantes, Nantes; Hôpital Haut-Lévêque, Centre Hospitalier Universitaire Bordeaux, Bordeaux; Centre Hospitalier Universitaire Dijon, Dijon; Institut Paoli Calmettes, Marseille; Centre Henri Becquerel, Rouen; Centre Hospitalier Universitaire Nancy, Nancy; Hôpital Claude Huriez, Centre Hospitalier Régional Universitaire de Lille, and Centre Hospitalier Universitaire, Lille; Hôpital Avicenne, Bobigny; Institut de Cancérologie et Hématologie, Brest; Hôpital Edouard Herriot, Lyon; Centre Hospitalier, La Roche-sur-Yon; Hôpital Bretonneau, Tours; Centre Hospitalier Universitaire, Strasbourg; Institut Curie, Paris, France; and Millennium Pharmaceuticals, Cambridge, MA.

Corresponding author: Jean-Luc Harousseau, MD, Centre René Gauducheau, Bd Jacques Monod, 44805 Nantes/St. Herblain, France; e-mail: jl-harousseau@nantes.fnclcc.fr.

ABSTRACT

Purpose
To compare efficacy and safety of bortezomib plus dexamethasone and vincristine plus doxorubicin plus dexamethasone (VAD) as induction before stem-cell transplantation in previously untreated myeloma.

Patients and Methods
Four hundred eighty-two patients were randomly assigned to VAD (n = 121), VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation (n = 121), bortezomib plus dexamethasone (n = 121), or bortezomib plus dexamethasone plus DCEP (n = 119), followed by autologous stem-cell transplantation. Patients not achieving very good partial response (VGPR) required a second transplantation. The primary end point was postinduction complete response/near complete response (CR/nCR) rate.

Results
Postinduction CR/nCR (14.8% *v* 6.4%), at least VGPR (37.7% *v* 15.1%), and overall response (78.5% *v* 62.8%) rates were significantly higher with bortezomib plus dexamethasone versus VAD; CR/nCR and at least VGPR rates were higher regardless of disease stage or adverse cytogenetic abnormalities. Response rates were similar in patients who did and did not receive DCEP. Post first transplantation, CR/nCR (35.0% *v* 18.4%) and at least VGPR (54.3% *v* 37.2%) rates remained significantly higher with bortezomib plus dexamethasone. Median progression-free survival (PFS) was 36.0 months versus 29.7 months (*P* = .064) with bortezomib plus dexamethasone versus VAD; respective 3-year survival rates were 81.4% and 77.4% (median follow-up, 32.2 months). The incidence of severe adverse events appeared similar between groups, but hematologic toxicity and deaths related to toxicity (zero *v* seven) were more frequent with VAD. Conversely, rates of grade 2 (20.5% *v* 10.5%) and grades 3 to 4 (9.2% *v* 2.5%) peripheral neuropathy during induction through first transplantation were significantly higher with bortezomib plus dexamethasone.

Conclusion
Bortezomib plus dexamethasone significantly improved postinduction and post-transplantation CR/nCR and at least VGPR rates compared with VAD and resulted in a trend for longer PFS. Bortezomib plus dexamethasone should therefore be considered a standard of care in this setting.

J Clin Oncol 28. © 2010 by American Society of Clinical Oncology

INTRODUCTION

High-dose melphalan therapy plus autologous stem-cell transplantation (HDT-ASCT) is a standard of care for previously untreated multiple myeloma (MM) patients age ≤ 65 years and results in a median overall survival (OS) of 4 to 6 years.[1-4] Tandem transplantation offers better outcome than single transplantation in patients not achieving a complete response/near complete response (CR/nCR)[2] or at least very good partial response (VGPR) after first transplantation.[4] Overall, in the context of transplantation, achievement of CR or VGPR is associated with improved

progression-free survival (PFS) and OS.[5,6] Achievement of CR or at least VGPR therefore represents a major objective of treatment for previously untreated MM.[7,8]

Historically, vincristine, doxorubicin, and dexamethasone (VAD) has been a standard for induction therapy before HDT-ASCT[2,4,9-12]; however, it typically results in CR rates < 10%.[10-13] More active induction regimens may result in increased at least VGPR rates, leading to increased at least VGPR rates post first transplantation and improved long-term outcomes. Moreover, improving at least VGPR rates post first transplantation could obviate the need for a second transplantation in an increased number of patients.[2,4] The novel agents bortezomib, thalidomide, and lenalidomide have demonstrated substantial activity in both previously untreated and relapsed MM, with high rates of response and at least VGPR in combination with standard MM agents and regimens.[14,15] Furthermore, the introduction of novel agents in first-line therapy has improved PFS and OS in the nontransplantation setting.[16,17]

An Intergroupe Francophone du Myélome (IFM) phase II study investigated bortezomib plus dexamethasone as induction before transplantation in 48 patients with previously untreated MM.[18] The response rate was 67%, including 21% CR/nCR and 31% at least VGPR. This translated into a 55% post-transplantation at least VGPR rate. Toxicities were generally mild to moderate and proved manageable; there was no treatment-related mortality.[18] Other studies of induction with bortezomib and dexamethasone have shown similarly high levels of activity.[19-22]

The IFM therefore conducted this phase III study to compare the efficacy and safety of VAD and bortezomib plus dexamethasone as induction therapy before HDT-ASCT and to evaluate the impact of postinduction consolidation therapy. The study aimed to determine whether bortezomib plus dexamethasone resulted in a higher postinduction CR/nCR rate compared with VAD and whether this produced improved response rates and outcomes post-transplantation.

PATIENTS AND METHODS

Patients

Eligible patients were age ≤ 65 years and had untreated symptomatic MM with measurable paraprotein in serum (> 10 g/L) or urine (> 0.2 g/24 h). Key inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, life expectancy ≥ 2 months, and adequate renal (no end-stage renal failure requiring dialysis), hematologic (platelets ≥ 50 × 10^9/L, neutrophils ≥ 0.75 × 10^9/L), and hepatic (bilirubin ≤ 3× upper limit of normal, AST and ALT ≤ 4× upper limit of normal) function. Key exclusion criteria included confirmed amyloidosis, HIV positivity, history of other malignancy (other than basal cell carcinoma and carcinoma of the cervix in situ), uncontrolled diabetes, and grade ≥ 2 peripheral neuropathy (National Cancer Institute Common Toxicity Criteria [NCI-CTC] v2.0). All patients provided written informed consent. The study was approved by the relevant national health authority agency and the Ethics Committee of the University of Nantes and was conducted in accordance with the International Conference on Harmonization guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki.

Study Design

This open-label phase III study was conducted at 89 sites in France, Belgium, and Switzerland between August 9, 2005, and January 18, 2008. Data cutoff date for this report was June 5, 2009. Patients were centrally randomly assigned (1:1:1:1) to receive VAD plus no consolidation (arm A1), VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consol-

idation (arm A2), bortezomib plus dexamethasone with no consolidation (arm B1), or bortezomib plus dexamethasone plus DCEP consolidation (arm B2). Randomization was stratified by baseline β_2-microglobulin (> 3 v ≤ 3 mg/L) and presence of chromosome 13 abnormalities by fluorescent in situ hybridization analysis.

VAD comprised four 4-week cycles of vincristine 0.4 mg/d and doxorubicin 9 mg/m²/d by continuous infusion days 1 to 4 plus dexamethasone 40 mg orally days 1 to 4 (all cycles) and days 9 to 12 and days 17 to 20 (cycles 1 and 2). Bortezomib plus dexamethasone comprised four 3-week cycles of bortezomib 1.3 mg/m² intravenously days 1, 4, 8, and 11 plus dexamethasone 40 mg days 1 to 4 (all cycles) and days 9 to 12 (cycles 1 and 2). DCEP comprised two 4-week cycles of dexamethasone 40 mg days 1 to 4 plus cyclophosphamide 400 mg/m², etoposide 40 mg/m², and cisplatin 15 mg/m²/d by continuous infusion days 1 to 4. Recommended concomitant medications included bisphosphonates (pamidronate 90 mg, zoledronate 4 mg) monthly until first transplantation, plus antibiotics, antifungal agents, and antiviral prophylaxis in accordance with local practice.

Stem-cell mobilization was undertaken with granulocyte colony-stimulating factor (G-CSF) 10 μg/kg/d from day 15, induction cycle 3. If collection was inadequate, a second mobilization was undertaken with cyclophosphamide 3 g/m² plus G-CSF 5 μg/kg/d after induction cycle 4. Target yield was 5 × 10⁶ CD34⁺ cells/kg. Conditioning for the first transplantation consisted of melphalan 200 mg/m². A second transplantation was not conducted for patients achieving at least VGPR. Patients achieving partial response (PR) and with an HLA-identical donor could undergo reduced-intensity conditioning allogeneic stem-cell transplantation (protocol IFM 2005-03). Patients achieving less than PR or those achieving PR but with no HLA-identical donor could undergo a second autologous procedure. All patients achieving at least PR post-transplantation were to receive 2 months consolidation with lenalidomide followed by lenalidomide maintenance or placebo on protocol IFM 2005-02.

Dose modifications were required for specified hematologic and non-hematologic adverse events (AEs). Patients with febrile neutropenia during induction had treatment discontinued until fever abated; treatment was discontinued for any grade 4 hematologic toxicity until neutrophils were > 0.75 × 10⁹/L and platelets were > 50 × 10⁹/L. Bortezomib-associated peripheral neuropathy was managed according to established guidelines.[23] For all other study drug–related grades 3 and 4 AEs, the agent responsible was withdrawn until complete recovery and was reinitiated at a reduced dose.

Assessments

The primary end point was postinduction CR/nCR rate. The study started before publication of the international uniform criteria,[24] which incorporated nCR within VGPR; we therefore also report at least VGPR rate as a relevant efficacy parameter. Secondary end points included postinduction overall response rate, CR/nCR rate with and without DCEP consolidation, CR/nCR and at least VGPR rates post first transplantation, proportions of patients requiring a second transplantation, and safety and toxicity of induction.

Response was evaluated by investigators according to modified European Group for Blood and Marrow Transplantation (EBMT) criteria,[25] including additional categories of nCR (CR but immunofixation-positive)[26] and VGPR (serum M-protein reduction ≥ 90%; urine light chain < 100 mg/24 h).[24] Responses were determined postinduction, post-DCEP, and after first and second transplantation; response assessments were confirmed by an independent review committee. Blood and 24-hour urine samples were taken at baseline, before each induction/consolidation cycle, 4 weeks after the last induction/consolidation cycle, at transplantation, and 1 to 3 months post-transplantation. In patients with 100% M-protein reduction by electrophoresis, determination of CR required immunofixation and bone marrow examination. EBMT criteria require response confirmation after 6 weeks; however, transplantation was not delayed to confirm postinduction/consolidation response. AEs were graded by NCI-CTC v2.0.

Statistical Analysis

Approximately 480 patients were to be enrolled to ensure 440 patients for analysis (110 in each arm; 220 receiving VAD or bortezomib plus dexamethasone induction). This provided 80% power (two-sided $\alpha = .05$) to detect a 10% difference in CR/nCR rate postinduction, assuming rates of 20% with bortezomib plus dexamethasone and 10% with VAD. It also provided 80% power (two-sided $\alpha = .05$) to demonstrate a 15% CR/nCR benefit with the addition of DCEP consolidation to VAD (10% to 25%) or bortezomib plus dexamethasone (20% to 35%).

Comparisons of response rates between patients receiving VAD or bortezomib plus dexamethasone, including the primary efficacy analysis of CR/nCR rate, were performed using a χ^2 test, as were comparisons of response rates between patients receiving or not receiving DCEP. Comparisons of time-to-event data were performed using the log-rank test; distributions were estimated using Kaplan-Meier methodology. PFS was defined as time from treatment start to progression, relapse, or death. Safety was evaluated in all patients who received at least one dose of study drug. Rates of AEs were compared between patients receiving VAD or bortezomib plus dexamethasone using the Cochran-Mantel-Haenszel χ^2 test adjusted for stratification factors.

RESULTS

Patient Characteristics and Disposition

A total of 493 patients were enrolled, and 482 were randomly assigned; 242 received VAD induction (121, A1; 121, A2) and 240 received bortezomib plus dexamethasone (121, B1; 119, B2). Patient disposition and flow through the protocol is shown in Figure 1. Baseline characteristics are summarized in Table 1. No significant differences were seen between groups. Overall, 57.5% of patients had

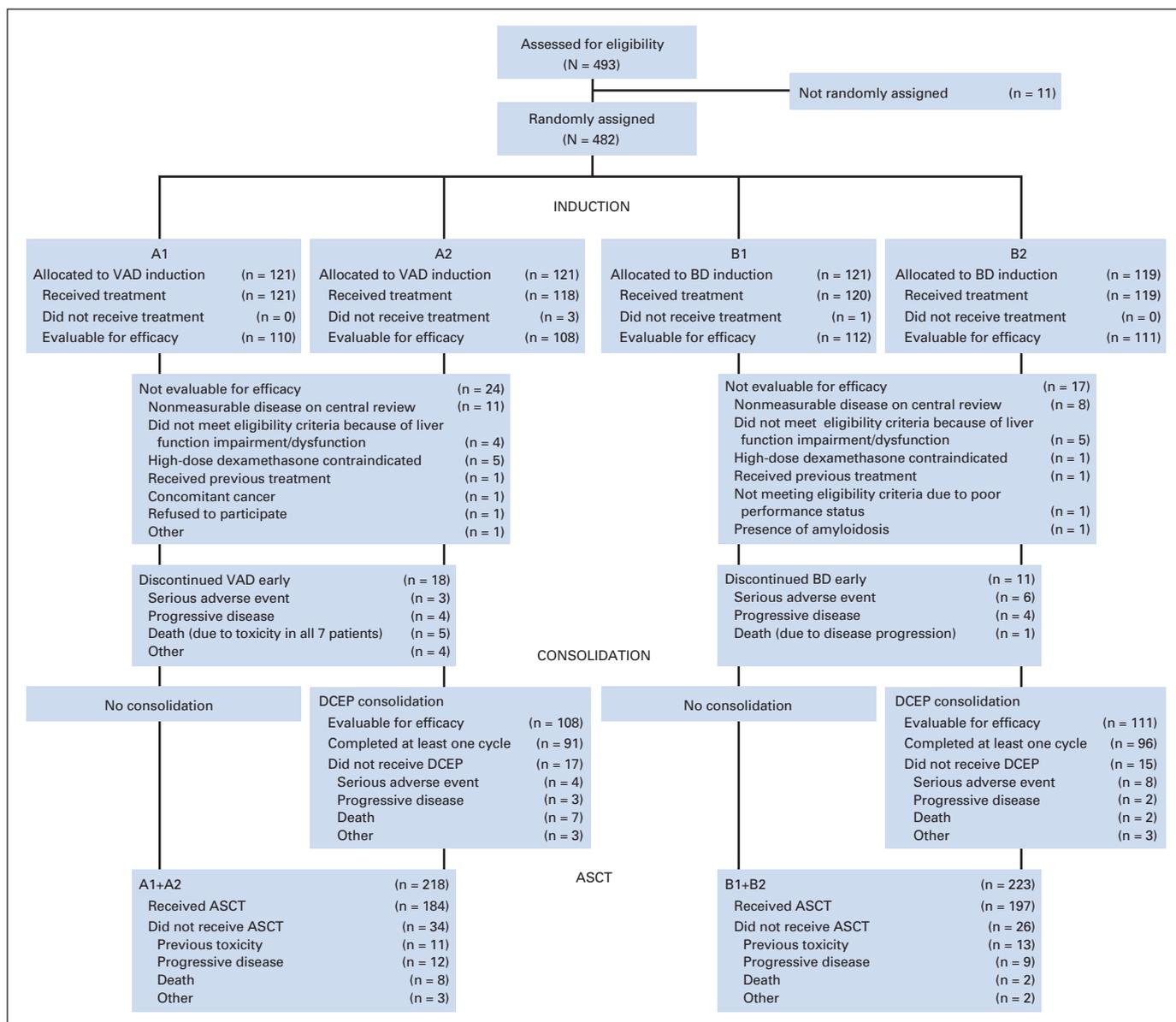**Fig 1.** Diagram of patient disposition and patient flow through protocol. VAD, vincristine plus doxorubicin plus dexamethasone; BD, bortezomib plus dexamethasone; DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin; A1, VAD plus no consolidation; A2, VAD plus DCEP consolidation; B1, BD with no consolidation; B2, BD plus DCEP consolidation; ASCT, autologous stem-cell transplantation.

Table 1. Baseline Patient Demographics and Disease Characteristics Overall and by Induction Treatment Received

Characteristics	All Patients (N = 482)		VAD (A1 + A2) (n = 242)		Bortezomib Plus Dexamethasone (B1 + B2) (n = 240)		P
	No.	%	No.	%	No.	%	
Male	266	55.2	127	52.5	139	57.9	.23
Mean age, years	55.6		55.8		55.4		.53
Median	57.1		57.1		57.2		
ISS stage							.73
I	199	41.3	97	40.1	102	42.5	
II	163	33.8	82	33.9	81	33.8	
III	106	22.0	54	22.3	52	21.7	
Not determined	14	2.9	9	3.7	5	2.1	
β_2-microglobulin > 3 mg/L	277	57.5	140	57.9	137	57.1	.86
del(13) by FISH	204	42.3	103	42.6	101	42.1	.92
t(4;14) and/or del(17p)	69	14.3	29	12.0	40	16.7	.14
Mean hemoglobin, g/dL	10.9		10.9		10.9		.97
Median	10.8		10.8		10.9		
Mean creatinine, μmol/L	103.5		100.6		106.4		.32
Median	87.0		87.0		87.0		
Mean calcium, μmol/L	2.4		2.4		2.4		.25
Medain	2.3		2.3		2.4		

Abbreviations: VAD, vincristine plus doxorubicin plus dexamethasone; A1, VAD plus no consolidation; A2, VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation; B1, bortezomib plus dexamethasone (BD) with no consolidation; B2, BD plus DCEP consolidation; ISS, International Staging System[27]; FISH, fluorescent in situ hybridization.

β_2-microglobulin > 3 mg/L, with 22% having International Staging System (ISS)[27] stage III myeloma; 42.3% had chromosome 13 deletion by fluorescent in situ hybridization. In the VAD and bortezomib plus dexamethasone groups, t(4;14) and/or del(17p) were seen in 12.0% and 16.7% of patients, respectively (P = .14).

Response to Induction and Consolidation

The evaluable population included 441 patients, 218 who received VAD (110, A1; 108, A2) and 223 who received bortezomib plus dexamethasone (112, B1; 111, B2); the reasons for exclusion of 24 and 17 patients, respectively, are shown in Figure 1. Postinduction CR/nCR rate was significantly higher following induction with bortezomib plus dexamethasone versus VAD (14.8% v 6.4%; P = .004); similarly, at least VGPR (37.7% v 15.1%; P < .001) and overall response rates were significantly higher (Table 2).

Significantly higher at least VGPR rates and consistently higher CR/nCR rates were seen with bortezomib plus dexamethasone versus VAD regardless of ISS disease stage and in patient subgroups defined by cytogenetic abnormalities (Table 2). The at least VGPR and CR/nCR rates were similar with bortezomib plus dexamethasone for patients with stage I, II, or III disease, whereas rates with VAD decreased with increasing disease stage. The at least VGPR and CR/nCR rates with bortezomib plus dexamethasone appeared somewhat higher in patients with del(13) versus no del(13) and were similar among patients with or without t(4;14) and/or del(17p).

Among the evaluable population, following induction with or without consolidation, CR/nCR (14.0% v 15.1%; P = .720) and at least VGPR (28.4% v 32.0%; P = .371) rates were similar in patients who were to receive DCEP (A2 + B2, n = 219) or not (A1 + B1, n = 222), by intent-to-treat analysis. Among patients who actually received DCEP (91, A2; 96, B2), CR/nCR and at least VGPR rates were

8.0% and 22.2% in A2 (v 8.2% and 15.4% in A1) and 26.0% and 50.0% in B2 (v 19.6% and 41.1% in B1). The at least VGPR rate was thus superior with bortezomib plus dexamethasone with no consolidation (B1) compared with VAD plus DCEP (A2).

Stem-Cell Mobilization and Transplantation

Stem cell yields of $> 2 \times 10^6$ CD34$^+$ cells/kg were achieved by 98% and 96% of VAD and bortezomib plus dexamethasone patients, respectively. Full data regarding stem-cell collection will be reported in depth elsewhere (Moreau et al, manuscript in preparation).

A total of 184 (84.4%) of 218 and 197 (88.3%) of 223 evaluable patients who received VAD and bortezomib plus dexamethasone induction, respectively, underwent transplantation. Post-transplantation response rates among the evaluable population are shown in Table 3. Post first transplantation, CR (16.1% v 8.7%; P = .016), CR/nCR (35.0% v 18.4%; P < .001), and at least VGPR (54.3% v 37.2%; P < .001) rates were significantly higher among patients who received bortezomib plus dexamethasone versus VAD. Overall, including responses post second transplantation, CR/nCR (39.5% v 22.5%; P < .001) and at least VGPR (67.7% v 46.7%; P < .001) rates, respectively, were again significantly higher.

Among patients in whom transplantation was actually performed, overall response rate post first transplantation was 90.9% and 91.3% (P = .921) in patients who received bortezomib plus dexamethasone and VAD, respectively, and CR (18.3% v 10.3%; P = .020), CR/nCR (39.6% v 21.7%; P < .001), and at least VGPR (61.4% v 44.0%; P = .001) rates were significantly higher following bortezomib plus dexamethasone versus VAD. Consequently, per protocol, fewer patients who received bortezomib plus dexamethasone along with first transplantation (76 [38.6%] of 197 patients) were deemed to require a second transplantation versus the VAD group

Table 2. Response to Induction Therapy Overall and According to Baseline Disease Stage and Prognostic Factors

Patients	VAD (A1 + A2) (n = 242)		Bortezomib Plus Dexamethasone (B1 + B2) (n = 240)		
	No.	%	No.	%	P
Evaluable population	218		223		
ORR (at least PR)	137	62.8	175	78.5	< .001
At least VGPR	33	15.1	84	37.7	< .001
CR/nCR	14	6.4	33	14.8	.004
CR	3	1.4	13	5.8	.012
MR + SD	58	26.6	28	12.6	
PD	9	4.1	10	4.5	
Death	6	2.8	1	0.5	
Not assessable	8	3.7	9	4.0	
ORR and at least VGPR and CR/nCR response rates by disease stage					
ISS 1	97		102		
ORR	65	67.0	83	81.4	.017
At least VGPR	20	20.6	38	37.3	.001
CR/nCR	11	11.3	16	15.7	.325
ISS 2	82		81		
ORR	47	57.3	58	71.6	.059
At least VGPR	11	13.4	29	35.8	.001
CR/nCR	4	4.9	12	14.8	.044
ISS 3	54		52		
ORR	31	57.4	40	76.9	.034
At least VGPR	4	7.4	21	40.4	< .001
CR/nCR	0		7	13.5	.006
ORR, and at least VGPR and CR/nCR response rates by cytogenetics					
del(13) by FISH	103		101		
ORR	67	65.1	79	78.2	.037
At least VGPR	15	14.6	47	46.5	< .001
CR/nCR	6	5.8	21	20.8	.002
No del(13)	139		139		
ORR	80	57.6	106	76.3	.001
At least VGPR	21	15.1	42	30.2	.003
CR/nCR	9	6.5	14	10.1	.276
β_2-microglobulin > 3 mg/L and del(13)	65		63		
ORR	42	64.6	45	71.4	.409
At least VGPR	10	15.4	27	42.9	.001
CR/nCR	3	4.6	12	19.1	.011
t(4;14) and/or del(17p)	29		40		
ORR	17	58.6	28	70.0	.327
At least VGPR	5	17.2	16	40.0	.043
CR/nCR	1	3.5	7	17.5	.072
Neither t(4;14) nor del(17p)	213		200		
ORR	130	61.0	157	78.5	< .001
At least VGPR	31	14.6	73	36.5	< .001
CR/nCR	14	6.8	28	14.0	.013

NOTE. All response assessments were confirmed by an independent review committee.
Abbreviations: VAD, vincristine plus doxorubicin plus dexamethasone; A1, VAD plus no consolidation; A2, VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation; B1, bortezomib plus dexamethasone (BD) with no consolidation; B2, BD plus DCEP consolidation; ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR/nCR, complete response/near CR; MR, minimal response; SD, stable disease; PD, progressive disease; ISS, International Staging System; FISH, fluorescent in situ hybridization.

(103 [56%] of 184; P = .001); however, of these patients, only 41 (20.8%) and 50 (27.2%), respectively, actually received a second transplantation.

Subsequent Therapy

Post transplantation, 153 patients each from the VAD and bortezomib plus dexamethasone groups received further treatment; 127 (83.0%) and 140 (91.5%), respectively (P = .026), were enrolled onto protocol IFM 2005-02 and received lenalidomide consolidation before random assignment to lenalidomide maintenance or placebo. Additionally, four patients (2.9%) from each group received lenalidomide maintenance, and 15 (10.2%) VAD and eight (5.3%; P = .116) bortezomib plus dexamethasone patients received thalidomide maintenance.

Table 3. Response to First Transplantation and Overall at Least VGPR and CR/nCR Rates, Including Second Transplantation, Among All Evaluable Patients

Response	VAD (A1 + A2) (n = 218)		Bortezomib Plus Dexamethasone (B1 + B2) (n = 223)		P
	No.	%	No.	%	
Response to first transplantation					
ORR (at least PR)	168	77.1	179	80.3	.401
At least VGPR	81	37.2	121	54.3	< .001
CR/nCR	40	18.4	78	35.0	< .001
CR	19	8.7	36	16.1	.016
MR + SD + PD	8	3.7	6	2.7	
Death	2	0.9	1	0.5	
No transplantation	34	15.6	26	11.7	
Overall, including second transplantation					
At least VGPR	102	46.7	151	67.7	< .001
CR/nCR	49	22.5	88	39.5	< .001

NOTE. All response assessments were confirmed by an independent review committee.

Abbreviations: VGPR, very good partial response; CR/nCR, complete response/near CR; VAD, vincristine plus doxorubicin plus dexamethasone; A1, VAD plus no consolidation; A2, VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation; B1, bortezomib plus dexamethasone (BD) with no consolidation; B2, BD plus DCEP consolidation; ORR, overall response rate; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

Fig 2. (A) Progression-free survival and (B) overall survival according to induction therapy received for all randomized patients. VAD, vincristine plus doxorubicin plus dexamethasone.

Outcomes

Figure 2 shows PFS and OS in all 482 patients according to induction therapy received. The median PFS was 29.7 months among patients who received VAD versus 36.0 months among patients who received bortezomib plus dexamethasone induction, with 128 (52.9%) of 242 and 110 (45.8%) of 240 patients, respectively, having progressed (P = .064, or P = .057 if adjusted for initial stratification factors) after median follow-up of 31.2 months. Median OS has not been reached in either group after median follow-up of 32.2 months, with 45 (18.6%) of 242 patients in the VAD group and 40 (16.7%) of 240 patients in the bortezomib plus dexamethasone group having died (P = .508, or P = .572 if adjusted for initial stratification factors); respective 3-year OS rates were 77.4% and 81.4%.

Safety

The safety population comprised 239 patients in the VAD group (910 cycles) and 239 patients in the bortezomib plus dexamethasone group (930 cycles). Safety profiles during induction, including the most common hematologic and nonhematologic toxicities, are summarized in Table 4. Grade 3 to 4 anemia, neutropenia, and thrombosis were significantly more frequent in the VAD group. Seven deaths related to toxicity (2.9%) were recorded in the VAD group versus none in the bortezomib plus dexamethasone group (P = .02).

During induction, consolidation, and first transplantation, peripheral neuropathy (encompassing multiple AEs; Table 4 double-dagger footnote) was reported in 77 (32.2%) and 126 (52.7%; P < .001) patients who received VAD and bortezomib plus dexamethasone, respectively. Rates of grade 2 (10.5% v 20.5%;
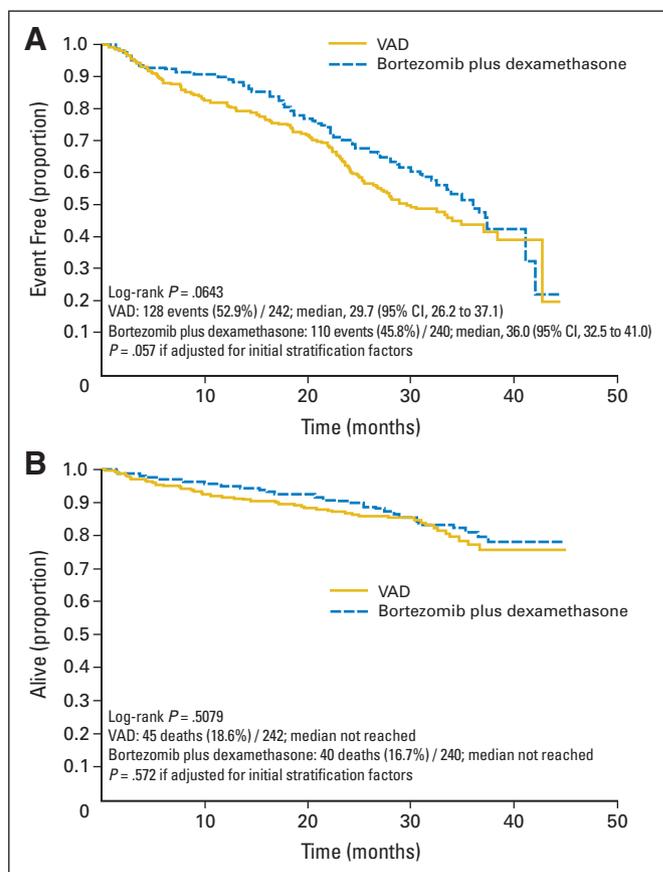
P = .003) and grade 3 to 4 (2.5% v 9.2%, P = .002) peripheral neuropathy were significantly higher in the bortezomib plus dexamethasone group.

Overall, 12 patients (seven infection, three hemorrhage, two progression) in the VAD group and two patients (one infection, one progression) in the bortezomib plus dexamethasone group died during protocol treatment, including seven and one during induction, one and zero during consolidation, and four and one during either transplantation, respectively.

DISCUSSION

The results of this IFM randomized phase III study demonstrate that among previously untreated MM patients age ≤ 65 years, induction therapy with bortezomib plus dexamethasone significantly improved both postinduction and post-transplantation rates of CR/nCR and at least VGPR compared with VAD, previously the standard of care in this setting. Notably, the at least VGPR rate achieved following the first transplantation in the bortezomib plus dexamethasone group is comparable with rates achieved after tandem transplantation in other studies.[4,9,10,12] Importantly, bortezomib plus dexamethasone was equally effective in patients with high-risk MM, including those with ISS stage III disease and poor-risk cytogenetic abnormalities. On intent-to-treat analysis of all

Table 4. Safety Profiles of Induction Therapy With VAD and Bortezomib Plus Dexamethasone, Including Most Common and Other Important Hematologic and Nonhematologic Toxicities

Variable	VAD (A1 + A2) (n = 239)				Bortezomib Plus Dexamethasone (B1 + B2) (n = 239)			
	No.	%	No.	%	No.	%	No.	%
Any AE	219	91.6*			231	96.7*		
Any grade ≥ 3 AE	110	46.0			112	46.9		
Any grade ≥ 4 AE	37	15.5			27	11.3		
Any serious AE	81	33.9			65	27.2		
Toxicity leading to study drug discontinuation or delay	32	13.4			44	18.4		
Toxicity leading to bortezomib dose reduction, No. of cycles					64 of 931	6.9		
Death related to toxicity	7	2.9*			0*			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
Hematologic toxicities								
Anemia	51	21.3	21	8.8*	38	15.9	10	4.2*
Neutropenia	33	13.8*	24	10.0*	19	8.0*	12	5.0*
Thrombocytopenia	11	4.6*	3	1.3	26	10.9*	7	2.9
Infections	91	38.1*	29	12.1	115	48.1*	21	8.8
Herpes zoster†	5	2.1*	—		22	9.2*	—	
Thrombosis	29	12.1*	13	5.4*	11	4.6*	4	1.7*
Nonhematologic toxicities								
Fatigue	50	20.9			68	28.5		
Rash	21	8.8			28	11.7		
GI symptoms	75	31.4			64	26.8		
Cardiac disorders	14	5.9			14	5.9		
Pneumopathy	15	6.3			8	3.4		
Peripheral neuropathy‡	67	28.0*			109	45.6*		
Peripheral neuropathy grade								
1	42	17.6			51	21.3		
2	19	8.0*			37	15.5*		
3-4	5	2.1*			17	7.1*		

Abbreviations: VAD, vincristine plus doxorubicin plus dexamethasone; A1, VAD plus no consolidation; A2, VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation; B1, bortezomib plus dexamethasone (BD) with no consolidation; B2, BD plus DCEP consolidation; AE, adverse event.

*$P < .05$ for comparison of AE rate between VAD and bortezomib plus dexamethasone.

†No antiviral prophylaxis for herpes zoster was specified in the protocol.

‡The following Medical Dictionary for Regulatory Activities (MedDRA)–preferred terms used by investigators were considered related to neurologic toxicity by the principal investigator and included in the totals for peripheral neuropathy: accommodation disorder, anosmia, areflexia, difficulty in walking, dysesthesia (no essential change), fall, formication, hypoesthesia, hyporeflexia, muscle spasms, neuralgia (not otherwise specified [NOS]), neuralgic amyotrophy, neurologic disorder NOS, pain in limb, paraparesis, paresthesia, peripheral neuropathy aggravated, peripheral motor neuropathy, peripheral neuropathy NOS, peripheral sensory neuropathy, polyneuropathy NOS, sensory loss, vertigo, vision blurred.

response-evaluable patients, use of DCEP consolidation postinduction did not have a significant impact on response rates. In patients who actually received DCEP, the benefit of adding consolidation to bortezomib plus dexamethasone was only marginal (50% v 41%, at least VGPR), and bortezomib plus dexamethasone with or without DCEP was superior to VAD plus DCEP, sugge-

sting that such additional treatment pretransplantation is not warranted.

Our data indicate that the better response rates postinduction and post-transplantation with bortezomib plus dexamethasone versus VAD translated into a trend toward longer PFS. It is important to note that this study was not designed to evaluate PFS and that the trend toward longer PFS in favor of the bortezomib plus dexamethasone group was seen despite slight imbalances between the groups, potentially favoring the VAD group in terms of improved PFS in the proportions of patients with poor-risk cytogenetics and the proportions of patients receiving a second transplantation. In addition, in randomized studies such as ours, it may be difficult to assess the impact of induction treatment on PFS when patients receive different post-transplantation treatment. Regarding OS, no significant difference is apparent after median follow-up of 32.2 months, and the number of deaths is too low to draw any statistically valid conclusions, as might be expected in this population in which median OS is 5 to 6 years.[1-4] OS comparisons may also be confounded by the effect of subsequent therapy.

Bortezomib plus dexamethasone appeared generally well tolerated, reflecting our phase II experience,[18] with zero deaths related to toxicity versus seven deaths related to toxicity in the VAD group within the four induction cycles. With bortezomib, there were significantly higher incidences of grades 2 to 4 peripheral neuropathy from induction through first transplantation compared with those in the VAD group. Nevertheless, these rates appeared similar to those reported in other studies of bortezomib alone or in combination.[18,21,22,28-31] Additionally, other studies of bortezomib plus dexamethasone have shown this toxicity to be reversible in the majority of patients.[18,32] When bortezomib is given in combination with dexamethasone or with chemotherapy, lower doses (1.0 mg/m^2 v 1.3 mg/m^2) or weekly administration of bortezomib may be associated with a lower incidence of peripheral neuropathy, while retaining substantial, although possibly somewhat reduced, efficacy.[22,30,32-34] Finally, 96% of patients treated with bortezomib plus dexamethasone yielded sufficient CD34$^+$ cells to undergo at least one transplantation, although stem-cell collection was primed with G-CSF only.

The response rates with VAD in our study appear comparable to those in previous reports,[4,35] while response rates with bortezomib plus dexamethasone appear favorable or comparable to those from randomized studies of other novel-agent-plus-dexamethasone induction regimens. In two phase III studies, thalidomide plus dexamethasone resulted in an overall response rate of 63% and CR rates of 4% to 7.7%,[36,37] with one study reporting an at least VGPR rate of 43.8% after a median duration of therapy of 6.9 months.[37] In a study of thalidomide plus dexamethasone versus VAD, the postinduction at least VGPR rates were 24.7% versus 7.3% ($P = .0027$); however, this difference was lost post-transplantation, with at least VGPR rates increasing to 44.4% and 41.7% ($P = .87$), respectively.[38] In the ECOG E4A03 phase III study of lenalidomide plus high-dose or low-dose dexamethasone,[39] overall response rates of 79% and 68%, respectively, were reported after four cycles of induction. Preliminary results from phase III studies of triplet induction regimens including bortezomib, doxorubicin, and dexamethasone[40]; cyclophosphamide, thalidomide, and dexamethasone[41]; and thalidomide, doxorubicin, and dexamethasone[35] seem to show similar response rates to those achieved with bortezomib plus dexamethasone. In contrast, response

rates appeared higher in two phase III studies of bortezomib, thalidomide, and dexamethasone (VTD),[28,42] and in early-phase studies of bortezomib, lenalidomide, and dexamethasone[43,44]; however, only randomized studies versus bortezomib plus dexamethasone would be able to confirm this.

In conclusion, bortezomib plus dexamethasone should now be considered a standard induction treatment before transplantation to which other regimens, including novel agents, should be compared. Triplet combinations using lower bortezomib doses might be as effective and better tolerated. An ongoing randomized trial (IFM 2007-02)[45] is evaluating bortezomib plus dexamethasone versus a VTD regimen employing bortezomib 1.0 mg/m^2 and thalidomide 100 mg dosing.

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: Iain Webb, Millennium Pharmaceuticals (C) **Consultant or Advisory Role:** Jean-Luc Harousseau, Celgene (C), Janssen-Cilag (C), Proteolix (C); Michel Attal, Celgene (C), Janssen-Cilag (C); Gerald Marit, Celgene (U); Mohamad Mohty, Genzyme (C), Janssen-Cilag (C), Amgen (C); Thierry Facon, Celgene (C), Janssen-Cilag (C); Philippe Moreau, Celgene (C), Janssen-Cilag (C), Proteolix (C) **Stock Ownership:** None **Honoraria:** Jean-Luc Harousseau, Celgene, Janssen-Cilag, Amgen, Novartis, Millennium Pharmaceuticals; Michel Attal, Celgene, Janssen-Cilag; Hervé Avet-Loiseau, Janssen-Cilag, Celgene; Gerald Marit, Janssen-Cilag; Mohamad Mohty, Genzyme, Janssen-Cilag, Amgen; Cyrille Hulin, Celgene, Janssen-Cilag; Thierry Facon, Celgene, Janssen-Cilag; Frédéric Maloisel, Amgen; Philippe Moreau, Celgene, Mundipharma, Janssen-Cilag **Research Funding:** Mohamad Mohty, Genzyme, Amgen **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Jean-Luc Harousseau, Michel Attal, Thierry Facon, Philippe Moreau
Financial support: Iain Webb
Administrative support: Iain Webb, Claire Mathiot, Philippe Moreau
Provision of study materials or patients: Michel Attal, Gerald Marit, Denis Caillot, Mohamad Mohty, Pascal Lenain, Cyrille Hulin, Thierry Facon, Philippe Casassus, Mauricette Michallet, Hervé Maisonneuve, Lotfi Benboubker, Frédéric Maloisel, Philippe Moreau
Collection and assembly of data: Jean-Luc Harousseau, Marie-Odile Petillon, Claire Mathiot, Philippe Moreau
Data analysis and interpretation: Jean-Luc Harousseau, Hervé Avet-Loiseau, Claire Mathiot, Philippe Moreau
Manuscript writing: Jean-Luc Harousseau, Michel Attal
Final approval of manuscript: Jean-Luc Harousseau, Michel Attal, Hervé Avet-Loiseau, Gerald Marit, Denis Caillot, Mohamad Mohty, Pascal Lenain, Cyrille Hulin, Thierry Facon, Philippe Casassus, Mauricette Michallet, Hervé Maisonneuve, Lotfi Benboubker, Frédéric Maloisel, Marie-Odile Petillon, Iain Webb, Claire Mathiot, Philippe Moreau

REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma: Intergroupe Français du Myélome. N Engl J Med 335:91-97, 1996

2. Cavo M, Tosi P, Zamagni E, et al: Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol 25:2434-2441, 2007

3. Child JA, Morgan GJ, Davies FE, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 348:1875-1883, 2003

4. Attal M, Harousseau JL, Facon T, et al: Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 349:2495-2502, 2003

5. Harousseau JL, Attal M, Avet-Loiseau H: The role of complete response in multiple myeloma. Blood 114:3139-3146, 2009

6. van de Velde HJ, Liu X, Chen G, et al: Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica 92:1399-1406, 2007

7. Harousseau JL, Attal M, Moreau P, et al: Should CR achievement be a major treatment objective? Haematologica 92:36-37, 2007 (abstr S6.1)

8. Harousseau JL, Avet-Loiseau H, Attal M, et al: Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: Long-term analysis of the IFM 99-02 and 99-04 trials. J Clin Oncol 27:5720-5726, 2009

9. Garban F, Attal M, Michallet M, et al: Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 107:3474-3480, 2006

10. Barlogie B, Jagannath S, Desikan KR, et al: Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 93:55-65, 1999

11. Barlogie B, Kyle RA, Anderson KC, et al: Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: Final results of phase III US Intergroup Trial S9321. J Clin Oncol 24:929-936, 2006

12. Barlogie B, Jagannath S, Vesole DH, et al: Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood 89:789-793, 1997

13. Cavo M, Zamagni E, Tosi P, et al: Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood 106:35-39, 2005

14. Richardson PG, Mitsiades C, Schlossman R, et al: New drugs for myeloma. Oncologist 12:664-689, 2007

15. San-Miguel J, Harousseau JL, Joshua D, et al: Individualizing treatment of patients with myeloma in the era of novel agents. J Clin Oncol 26:2761-2766, 2008

16. Facon T, Mary JY, Hulin C, et al: Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): A randomised trial. Lancet 370:1209-1218, 2007

17. 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

18. Harousseau JL, Attal M, Leleu X, et al: Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: Results of an IFM phase II study. Haematologica 91:1498-1505, 2006

19. Na Nakorn T, Watanaboonyongcharoen P, Niparuck P, et al: Bortezomib with dexamethasone as induction therapy in newly diagnosed multiple myeloma: A preliminary study in Thai patients. Haematologica 92:181, 2007 (suppl 2; abstr PO-724)

20. Rosiñol L, Oriol A, Mateos MV, et al: Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: Efficacy and clinical implications of tumor response kinetics. J Clin Oncol 25:4452-4458, 2007

21. Corso A, Barbarabo L, Mangiacavalli S, et al: Bortezomib plus dexamethasone can improve stem cell collection and overcome the need for additional chemotherapy before autologous transplant in patients with myeloma. Leuk Lymphoma 51:236-242, 2010

22. Jagannath S, Durie BG, Wolf JL, et al: Extended follow-up of a phase 2 trial of bortezomib alone and in combination with dexamethasone for the frontline treatment of multiple myeloma. Br J Haematol 146:619-626, 2009

23. 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

24. Durie BG, Harousseau JL, Miguel JS, et al: International uniform response criteria for multiple myeloma. Leukemia 20:1467-1473, 2006

25. 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 102:1115-1123, 1998

26. Richardson PG, Barlogie B, Berenson J, et al: A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 348:2609-2617, 2003

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

28. Cavo M, Tacchetti P, Patriarca F, et al: A phase III study of double autotransplantation incorporating bortezomib/thalidomide/dexamethasone (VTD) or thalidomide/dexamethasone (TD) for multiple myeloma: Superior clinical outcomes with VTD compared to TD. Blood 114:148-149, 2009 (abstr 351)

29. Orlowski RZ, Nagler A, Sonneveld P, et al: Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression. J Clin Oncol 25:3892-3901, 2007

30. Popat R, Oakervee HE, Hallam S, et al: Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: Updated results after long-term follow-up. Br J Haematol 141:512-516, 2008

31. Richardson PG, Sonneveld P, Schuster MW, et al: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487-2498, 2005

32. Corso A, Mangiacavalli S, Varettoni M, et al: Bortezomib-induced peripheral neuropathy in multiple myeloma: A comparison between previously treated and untreated patients. Leuk Res 34:471-474, 2010

33. Mateos M-V, Oriol A, Martinez J, et al: A prospective, multicenter, randomized trial of bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years. Blood 114: 3-4, 2009 (abstr 3)

34. Palumbo A, Bringhen S, Rossi D, et al: Bortezomib, melphalan, prednisone and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide for initial treatment of elderly multiple myeloma patients. Blood 114:58, 2009 (abstr 128)

35. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, et al: Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. Haematologica 93:124-127, 2008

36. Rajkumar SV, Blood E, Vesole D, et al: Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 24:431-436, 2006

37. Rajkumar SV, Rosiñol L, Hussein M, et al: Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol 26:2171-2177, 2008

38. Macro M, Divine M, Uzunhan Y, et al: Dexamethasone + thalidomide (Dex/Thal) compared to VAD as a pre-transplant treatment in newly diagnosed multiple myeloma (MM): A randomized trial. Blood 108:22a, 2006 (abstr 57)

39. Rajkumar SV, Jacobus S, Callander NS, et al: Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomised controlled trial. Lancet Oncol 11:29-37, 2010

40. Sonneveld P, van der Holt B, Schmidt-Wolf IGH, et al: First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycine, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM). Haematologica 94:191, 2009 (suppl 2; abstr 0473)

41. Morgan GJ, Davies FE, Owen RG, et al: Thalidomide combinations improve response rates: Results from the MRC IX study. Blood 110:1051A, 2007 (abstr 3593)

42. Rosiñol L, Cibeira MT, Martinez J, et al: Thalidomide/dexamethasone (TD) vs. bortezomib (Velcade)/thalidomide/dexamethasone (VTD) vs. VBMCP/VBAD/Velcade as induction regimens prior autologous stem cell transplantation (ASCT) in multiple myeloma (MM): Results of a phase III PETHEMA/GEM trial. Blood 114:59, 2009 (abstr 130)

43. Kumar S, Flinn IW, Hari PN, et al: Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: Encouraging results from the multi-center, randomized, phase 2 EVOLUTION study. Blood 114:57-58, 2009 (abstr 127)

44. Richardson PG, Weller E, Lonial S, et al: Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood [epub ahead of print on April 12, 2010]

45. Harousseau J-L, Avet-Loiseau H, Facon T, et al: Bortezomib plus dexamethasone (VD) versus reduced-dose bortezomib plus thalidomide plus dexametason (VTD) as induction treatment prior to autologous stem-cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM). Blood 114:150, 2009 (abstr 354)

∎∎∎

Appendix

The following are Intergroupe Francophone du Myélome 2005-01 (IFM 2005-01) study investigators: France: Isabelle Leduc, Abbeville; Sylvie Cailleres, Aix; Bruno Royer, Amiens H; Valery Salle, Amiens MI; M. Dib, Angers; F. Orsini Piocelle, Annecy; François Boue, Antoine Beclere; Pauline Lionne-Huyghe, Arras; Gérard Lepeu, Avignon; Anne Banos, Bayonne; Jean Luc Dutel, Beauvais; Jean Fontan, Besancon; Philippe Rodon, Blois; Philippe Casassus, Bobigny; Gérald Marit, Bordeaux; Olivier Fitoussi, Bordeaux N; Hubert Orfeuvre, Bourg en Bresse; Christian Berthou, Brest; C. Fruchart, Caen CAC; Xavier Levaltier, Caen Polyclinic; Régis Kaphan, Cannes; Michel Maigre, Chartres; Bruno de Renzis, Clermont; Bruno Audhy, Colmar; Denis Caillot, Dijon; Marc Wetterwald, Dunkerque; Brigitte Pegourie, Grenoble; David Assouline, Grenoble Lemail; Hervé Maisonneuve, La Roche; Dominique Jacomy, Laval; J. Dugay, Le Mans CH; Eric Voog, Le Mans VH; Brigitte Dupriez, Lens; Joel Ceccaldi, Libourne; Thierry Facon, Lille; Emmanuelle Bourgeois, Lille St. Vincent; Philippe Moreau, Lorient; Catherine Sebban, Lyon CLB; Mauricette Michallet, Lyon EH; Catherine Traulle, Lyon PB; Anne Marie Stoppa, Marseille IPC; Véronique Dorvaux, Metz Bon Secours; Marc Galzin, Metz Legouest; Elena Loppinet, Metz Ste. Blandine; Alex Bellange, Morlaix; Jean Claude Eisenman, Mulhouse; Cyrille Hulin, Nancy; Nadine Morineau, Nantes CS; Philippe Moreau, Nantes CHU; Laurence Legros, Nice Hemato; Jean Gabriel Fuzibet, Nice Med Interne; Jean Michel Boulet, Orleans; Richard Delarue, Necker; Laurent

Garderet, St. Antoine; François Dreyfus, Cochin; Bernard Rio, Hotel Dieu; François Decaudin, Institut Curie; C. de Revel, Percy; Edouard Randriamalala, Poitiers; Riad Benramdane, Pontoise; Michel Laroche, Toulouse Rangueil; Brigitte Kolb, Reims; Thierry Lamy, Rennes Hemato; Bernard Grosbois, Rennes Med Int; Nadine Boullanger, Roanne; Isabelle Plantier, Roubaix; Pascal Lenain, Rouen; Patrick Morice, St. Brieuc; Jérome Jaubert, St. Etienne; Bruno Lioure, Strasbourg; Pierre de Jaureguiberry, Toulon; Michel Attal, Toulouse; Lotfi Benboubker, Tours; Nadia Ali Ammar, Troyes; Bruno Anglaret, Valence; Henry Jardel, Vannes; J.H. Bourhis, Villejuif IGR. Belgium: Nathalie Meuleman, Bordet; Chantal Doyen, Mont Godinne; Christiane Vekemans, St. Luc Bruxelles. Switzerland: Thomas Pabst, Berne; Daniel Rauch, Thun; Nicolas Keterrer, Lausanne; Christophe Driessen, St. Gallen; Marc Heizmann, Aarau; Thomas Matthes, Geneve.