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

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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 doxorubicin plus 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 (35.6% 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.

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)5 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.6-8 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-ASCT2-4,9-12; 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 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**

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 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) consolidation (arm A2), bortezomib plus dexamethasone with no consolidation (arm B1), or bortezomib plus dexamethasone plus DCEP consolidation (arm B2). Randomization was stratified by baseline β2-microglobulin (≥ 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 × 10^9 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 × 10^9/L and platelets were > 50 × 10^9/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 reinstituted 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).27 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 \( \alpha = 0.05 \)) 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 \( \alpha = 0.05 \)) 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 \( \chi^2 \) 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 \( \chi^2 \) 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

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**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.
Among the evaluable population, following induction with or without consolidation, CR/nCR (14.0% vs 15.1%; \( P = .720 \)) and at least VGPR (28.4% vs 32.0%; \( P = .371 \)) rates were similar in patients who received 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 (vs 8.2% and 15.4% in A1) and 26.0% and 50.0% in B2 (vs 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).

### 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% vs 6.4%; \( P = .004 \)); similarly, at least VGPR (37.7% vs 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).

### Stem-Cell Mobilization and Transplantation

Stem cell yields of > 2 x 10^9 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. Posttransplantation response rates among the evaluable population are shown in Table 3. Post first transplantation, CR (16.1% vs 8.7%; \( P = .016 \)), CR/nCR (35.0% vs 18.4%; \( P < .001 \)), and at least VGPR (54.3% vs 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% vs 22.5%; \( P < .001 \)) and at least VGPR (67.7% vs 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% vs 10.3%; \( P = .020 \)), CR/nCR (39.6% vs 21.7%; \( P < .001 \)), and at least VGPR (61.4% vs 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.
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 2. Response to Induction Therapy Overall and According to Baseline Disease Stage and Prognostic Factors

<table>
<thead>
<tr>
<th>Patients</th>
<th>VAD (A1 + A2) ((n = 242))</th>
<th>Bortezomib Plus Dexamethasone (B1 + B2) ((n = 240))</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Evaluable population</td>
<td>218</td>
<td>223</td>
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<tr>
<td>ORR (at least PR)</td>
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<td>.001</td>
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<tr>
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<td>33</td>
<td>.004</td>
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<td>CR</td>
<td>3</td>
<td>13</td>
<td>.012</td>
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<td>MR + SD</td>
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<td>28</td>
<td>12.6</td>
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<tr>
<td>PO</td>
<td>9</td>
<td>10</td>
<td>4.5</td>
</tr>
<tr>
<td>Death</td>
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<td>1</td>
<td>0.5</td>
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<tr>
<td>Not assessable</td>
<td>8</td>
<td>9</td>
<td>4.0</td>
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<tr>
<td>ORR and at least VGPR and CR/nCR response rates by disease stage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ISS 1</td>
<td>97</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>65</td>
<td>83</td>
<td>81.4</td>
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<tr>
<td>At least VGPR</td>
<td>20</td>
<td>38</td>
<td>37.3</td>
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<tr>
<td>CR/nCR</td>
<td>11</td>
<td>16</td>
<td>15.7</td>
</tr>
<tr>
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</tr>
<tr>
<td>ORR</td>
<td>47</td>
<td>58</td>
<td>71.6</td>
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<tr>
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<td>29</td>
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<tr>
<td>CR/nCR</td>
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<td>12</td>
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<tr>
<td>ORR</td>
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<tr>
<td>At least VGPR</td>
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<tr>
<td>CR/nCR</td>
<td>0</td>
<td>7</td>
<td>13.5</td>
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<td>ORR, and at least VGPR and CR/nCR response rates by cytogenetics</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>del(13) by FISH</td>
<td>103</td>
<td>101</td>
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<tr>
<td>ORR</td>
<td>67</td>
<td>79</td>
<td>78.2</td>
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<tr>
<td>At least VGPR</td>
<td>15</td>
<td>47</td>
<td>46.5</td>
</tr>
<tr>
<td>CR/nCR</td>
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<td>20.8</td>
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<td>ORR</td>
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<td>At least VGPR</td>
<td>21</td>
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<tr>
<td>CR/nCR</td>
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<td>14</td>
<td>10.1</td>
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<td>(\beta_2)-microglobulin &gt; 3 mg/L and del(13)</td>
<td>65</td>
<td>63</td>
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<tr>
<td>ORR</td>
<td>42</td>
<td>45</td>
<td>71.4</td>
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<tr>
<td>At least VGPR</td>
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<td>42.9</td>
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<tr>
<td>CR/nCR</td>
<td>3</td>
<td>12</td>
<td>19.1</td>
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<tr>
<td>t(4;14) and/or del(17p)</td>
<td>29</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>17</td>
<td>28</td>
<td>70.0</td>
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<tr>
<td>At least VGPR</td>
<td>5</td>
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<td>40.0</td>
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<td>CR/nCR</td>
<td>1</td>
<td>7</td>
<td>17.5</td>
</tr>
<tr>
<td>Neither t(4;14) nor del(17p)</td>
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<td>200</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>130</td>
<td>157</td>
<td>78.5</td>
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<tr>
<td>At least VGPR</td>
<td>31</td>
<td>73</td>
<td>36.5</td>
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<tr>
<td>CR/nCR</td>
<td>14</td>
<td>28</td>
<td>14.0</td>
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</tbody>
</table>

**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.
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 = .004, 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 128 patients who received VAD versus 36.0 months among patients who received bortezomib plus dexamethasone.

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

<table>
<thead>
<tr>
<th>Response to First Transplantation</th>
<th>Bortezomib Plus Dexamethasone</th>
<th>VAD (A1 + A2)</th>
<th>Dexamethasone (B1 + B2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, including second transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least VGPR</td>
<td>102</td>
<td>46.7</td>
<td>151</td>
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<tr>
<td>CR/nCR</td>
<td>49</td>
<td>22.5</td>
<td>88</td>
</tr>
<tr>
<td>Overall, including second transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least VGPR</td>
<td>168</td>
<td>77.1</td>
<td>179</td>
</tr>
<tr>
<td>At least VGPR, CR/nCR</td>
<td>81</td>
<td>37.2</td>
<td>121</td>
</tr>
</tbody>
</table>

**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 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.

The data are presented as number (%) of patients.

**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.
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% vs 41%, at least VGPR), and bortezomib plus dexamethasone with or without DCEP was superior to VAD plus DCEP, sug-
rates appeared higher in two phase III studies of bortezomib, thalidomide, and dexamethasone (VTD), and in early-phase studies of bortezomib, lenalidomide, and dexamethasone, 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) is evaluating bortezomib plus dexamethasone versus a VTD regimen employing bortezomib 1.0 mg/m² and thalidomide 100 mg dosing.

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