

Bortezomib As Induction Before Autologous Transplantation, Followed by Lenalidomide As Consolidation-Maintenance in Untreated Multiple Myeloma Patients

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Submitted March 2, 2009; accepted September 9, 2009; published online ahead of print at www.jco.org on January 4, 2010.

Supported by Fondazione Neoplasie Sangue Onlus, Associazione per lo Studio e la Cura delle Malattie del Sangue, Regione Piemonte, Ministero Università Ricerca Scientifica e Tecnologia, and Consiglio Nazionale delle Ricerche.

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

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0732-183X/10/2899-1/\$20.00

DOI: 10.1200/JCO.2009.22.7561

ABSTRACT

Purpose

To evaluate the effect of bortezomib as induction therapy before autologous transplantation, followed by lenalidomide as consolidation-maintenance in myeloma patients.

Patients and Methods

Newly diagnosed patients age 65 to 75 years were eligible. Induction (bortezomib, doxorubicin, and dexamethasone [PAD]) included four 21-day cycles of bortezomib (1.3 mg/m² on days 1, 4, 8, and 11), pegylated liposomal doxorubicin (30 mg/m² on day 4), and dexamethasone (40 mg/d; cycle 1: days 1 to 4, 8 to 11, and 15 to 18; cycles 2 to 4: days 1 to 4). Autologous transplantation was tandem melphalan 100 mg/m² (MEL100) and stem-cell support. Consolidation included four 28-day cycles of lenalidomide (25 mg/d on days 1 to 21 every 28 days) plus prednisone (50 mg every other day), followed by maintenance with lenalidomide (LP-L; 10 mg/d on days 1 to 21) until relapse. Primary end points were safety (incidence of grade 3 to 4 adverse events [AEs]) and efficacy (response rate).

Results

A total of 102 patients were enrolled. In a per-protocol analysis, after PAD, 58% of patients had very good partial response (VGPR) or better, including 13% with complete response (CR); after MEL100, 82% of patients had at least VGPR and 38% had CR; and after LP-L, 86% of patients had at least VGPR and 66% had CR. After median follow-up time of 21 months, the 2-year progression-free survival rate was 69%, and the 2-year overall survival rate was 86%. During induction, treatment-related mortality was 3%; grade 3 to 4 AEs included thrombocytopenia (17%), neutropenia (10%), peripheral neuropathy (16%), and pneumonia (10%). During consolidation-maintenance, grade 3 to 4 AEs were neutropenia (16%), thrombocytopenia (6%), pneumonia (5%), and cutaneous rash (4%).

Conclusion

Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance, is an effective regimen.

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

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy worldwide. Annually, in the United States and Europe, it causes nearly 11,000 and 19,000 deaths, respectively.^{1,2} The introduction of new drugs, such as thalidomide, bortezomib, and lenalidomide, has significantly improved overall response rates (ORRs), progression-free survival (PFS), and overall survival (OS). Patients who received these new drugs

had longer survival from relapse compared with patients who did not receive these new therapies (30.9 v 14.8 months, respectively; $P < .001$). Similarly, patients diagnosed in the past decade had a 50% improvement in OS compared with patients diagnosed before December 1996, when thalidomide was introduced (44.8 v 29.9 months, respectively; $P < .001$).³

The proteasome inhibitor bortezomib is an active agent in MM patients.⁴ In a randomized study, bortezomib plus dexamethasone was compared

with vincristine, doxorubicin, and dexamethasone as induction before autologous stem-cell transplantation (ASCT); bortezomib plus dexamethasone induced a significantly higher complete response (CR) rate and PFS.⁵ In another study, bortezomib with pegylated liposomal doxorubicin was superior to single-agent bortezomib.⁶ In a phase II study, the combination of bortezomib, doxorubicin, and dexamethasone (PAD) was evaluated as induction before ASCT; it also induced a high CR rate.⁷

Lenalidomide is less toxic and more potent than its parent drug thalidomide, and both drugs are active in patients with MM.⁸⁻¹⁰ In randomized trials, thalidomide has been administered as maintenance after ASCT. In some studies, addition of thalidomide improved PFS¹¹⁻¹²; in another study, the benefit of thalidomide maintenance was less evident.¹³ In a recent trial, a benefit of thalidomide maintenance was only seen in patients achieving less than a very good partial response (VGPR) after induction.¹⁴ Lenalidomide lacks the neurotoxic effects of thalidomide and represents an optimal agent to include in maintenance regimens.

These observations provided the rationale for investigating bortezomib as induction therapy and lenalidomide as consolidation-maintenance therapy in patients undergoing ASCT. Here, we report safety and efficacy data of bortezomib as induction therapy before reduced-intensity ASCT, followed by lenalidomide as consolidation-maintenance therapy in untreated elderly MM patients.

PATIENTS AND METHODS

Patients

From October 2005 to July 2007, 102 patients were enrolled from 17 Italian centers. Inclusion criteria were as follows: newly diagnosed MM; pa-

tients age 65 to 75 years or patients less than age 65 years who refused or were ineligible for high-dose therapy; measurable disease¹⁵; platelet count $\geq 100 \times 10^9/L$; absolute neutrophil count $\geq 1 \times 10^9/L$; corrected serum calcium ≤ 14 mg/dL; serum hepatic aminotransferase levels $\leq 2.5 \times$ the upper limit of normal (ULN); total bilirubin $\leq 1.5 \times$ the ULN; and creatinine clearance ≥ 30 mL/min. The institutional review boards at participating centers approved the study in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Study Design and Treatment

In this phase II, multicenter, noncomparative, open-label study, patients received induction with four 21-day PAD cycles (bortezomib 1.3 mg/m² on days 1, 4, 8, and 11; pegylated liposomal doxorubicin 30 mg/m² on day 4; and dexamethasone 40 mg/d on days 1 to 4, 8 to 11, and 15 to 18 in cycle 1 and on days 1 to 4 in cycles 2 to 4. Cyclophosphamide (3 g/m²) and granulocyte colony-stimulating factor (G-CSF; 10 μ g/kg) were used to mobilize stem cells. Melphalan was administered twice at the dose of 100 mg/m² (MEL100) followed by stem-cell reinfusion. Patients without progressive disease (PD) at 2 to 4 months after the second MEL100 dose received consolidation (lenalidomide plus prednisone [LP]) with four 28-day cycles of lenalidomide (25 mg/d; days 1 to 21 every 28 days) plus prednisone (50 mg every other day); thereafter, lenalidomide alone (L; 10 mg/d on days 1 to 21) was used as maintenance until relapse (LP-L; Fig 1). Acyclovir was recommended during bortezomib treatment. Aspirin (100 mg/d) was administered as anticoagulant prophylaxis during lenalidomide treatment.

The occurrence of grade 3 to 4 neutropenia for ≥ 7 days despite G-CSF, any other grade 4 hematologic adverse events (AEs), or any grade 3 nonhematologic toxicities required treatment interruption and subsequent dose reduction. A new cycle was allowed if the neutrophil count was $\geq 1 \times 10^9/L$, the platelet count was $\geq 50 \times 10^9/L$, and nonhematologic AEs were \leq grade 1. A 2-week delay was allowed without dose modification. If the start of a new cycle was delayed beyond 2 weeks, dose reduction was required; a delay beyond 4 weeks required discontinuation. Bortezomib-associated neuropathic pain and peripheral neuropathy were managed by established dose modifications.¹⁶

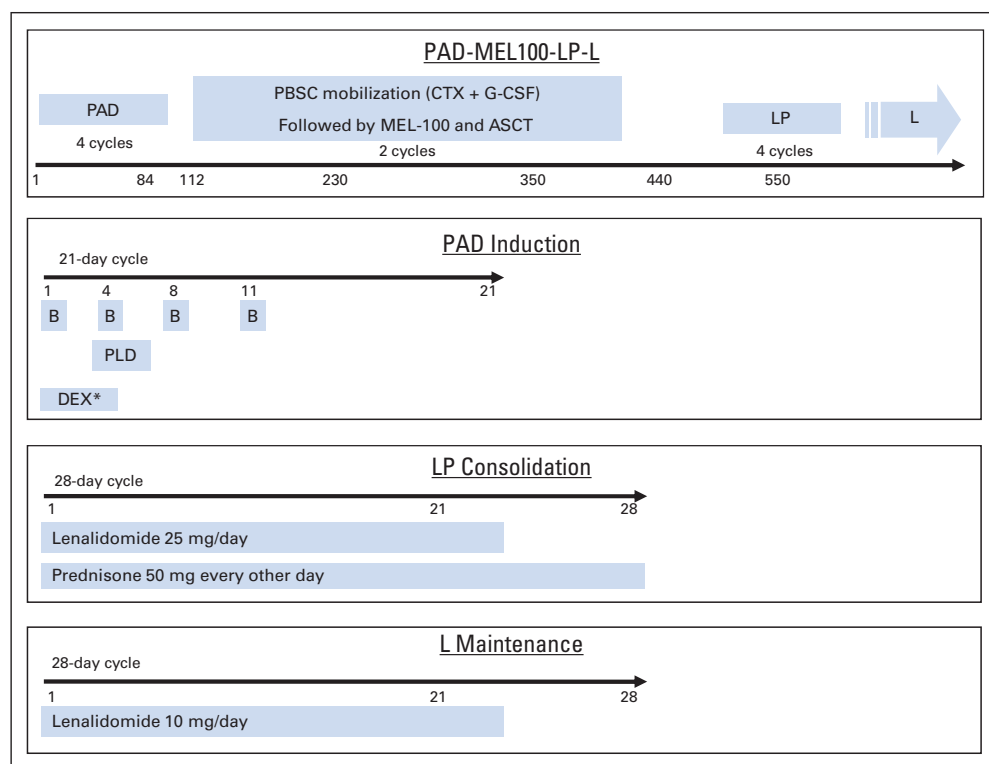


Fig 1. Treatment schedule. PAD, bortezomib, pegylated liposomal doxorubicin, and dexamethasone; CTX, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; PBSC, peripheral-blood stem cells; MEL100, melphalan; LP, lenalidomide plus prednisone; L, lenalidomide; PLD, pegylated doxorubicin 30 mg/m²; DEX, dexamethasone 40 mg/day; B, bortezomib 1.3 mg/m². (*) DEX days 1-4, 8-11, 15-18 on cycle 1.

Five lenalidomide dose reductions were allowed (20 mg/d, 15 mg/d, 10 mg/d, 15 mg every other day, and 5 mg every other day).

Assessment of Efficacy and Safety

Efficacy was assessed every 4 weeks. Safety was assessed weekly during PAD, every 2 weeks during LP consolidation, and monthly during maintenance. Treatment response was monitored using the standard International Myeloma Working Group Uniform Response Criteria.¹⁵ Time to progression was defined as time from enrollment until progression or relapse; deaths as a result of causes other than progression were censored. PFS was defined as time from enrollment until the date of progression, relapse, or death from any cause (whichever occurred first). OS was defined as time from enrollment until the date of death or the date the patient was last known to be alive.¹⁵ All AEs were assessed at each visit and graded according to the National Cancer Institute Common Criteria for Adverse Events (version 3).¹⁷

Fluorescence In Situ Hybridization Analysis

Fluorescence in situ hybridization analyses were performed on bone marrow plasma cells purified with anti-CD138-coated magnetic beads as previously described.^{18,19} Deletion of chromosome 13 (del13) was analyzed with an locus-specific identifier (LSI) 13 DNA probe; chromosome 17 deletion (del17) was detected with an LSI 17p13.1 probe combined with 17 α -satellite DNA centromere probe. LSI immunoglobulin H (IgH)/fibroblast growth factor receptor 3 dual fusion translocation probe (FGFR3, 4p16) was used for the detection of IgH/FGF3 fusion resulting from t(4;14)(p16;q32); LSI IgH/cyclin D1 (CCND1, 11q13) was used to detect IGH/CCND1 fusion resulting from t(11;14)(q13;q32), and LSI IgH/c-maf (MAF, 16q23) was used for the detection of the IgH/MAF fusion resulting from t(14;16)(q32;q23).

End Points and Statistical Analysis

The study was designed using Fleming’s method²⁰ with a one-sided type I error of 0.05 and statistical power of 80%. The expected CR rate with the experimental treatment was 25%; the CR rate with standard treatment was 15%. Primary end points were safety (grade 4 neutropenia for \geq 7 days, any other grade 4 hematologic toxicity, and any grade \geq 3 nonhematologic toxicity in < 30% of patients) and efficacy (CR rate \geq 15% after PAD plus MEL100 and \geq 25% after LP-L). Secondary end points were PFS and OS. All patients meeting eligibility criteria who had started the first cycle of therapy were evaluated for toxicity, response, and survival. Time-to-event estimates were determined using the Kaplan-Meier method²¹ and compared using the log-rank test. *P* values were corrected (*P_c*) using the Bonferroni correction for multiple comparisons. Analysis of PFS according to response rate was performed using the landmark analysis method (landmark point at 3 months from the start of treatment). Analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC). Times of observation were censored on January 30, 2009. Safety and efficacy analyses were performed on an intent-to-treat basis. The per-protocol analysis was performed to determine the ORR in all assigned participants who completed the PAD induction, the tandem MEL100 transplantation, or the LP-L consolidation-maintenance.

RESULTS

Patient Characteristics

Characteristics of the 102 enrolled patients are listed in Table 1. At the time of analysis, all patients completed the assigned MEL100 transplantation, 80 patients (78%) entered the LP consolidation, and 50 patients (49%) were evaluable at the L maintenance phase. Three of the 102 patients who received PAD as induction therapy died (diverticulitis, septic shock, and CNS bleeding). Four patients did not complete the assigned therapy because of AEs (grade 4 neuropathy, n = 2; bowel infarction, n = 1; and grade 3 hepatitis B reactivation, n = 1), two patients experienced PD; and one patient withdrew consent.

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients (N = 102)	%
Age, years		
Median	67	
Range	46-74	
\geq 70	26	26
Sex		
Male	53	52
Female	49	48
International Staging System stage		
I	48	47
II	30	29
III	12	12
Not available	12	12
Myeloma protein class		
IgG	57	56
IgA	23	23
Bence-Jones	20	20
Not available	2	2
Plasmacytoma	16	16
Bone marrow plasmacytosis, %		
Median	50	
Range	2-99	
Hemoglobin level, g/dL		
Median	11.2	
Range	5.4-17.6	
Albumin level, g/dL		
Median	4	
Range	1.6-5.7	
Creatinine level, mg/dL		
Median	0.95	
Range	0.45-2.5	
\geq 2 mg/dL	6	6
b ₂ -microglobulin, mg/L		
Median	3.0	
Range	0.5-22.7	
Cytogenetic abnormalities*		
Deletion of chromosome 13	50	63
Deletion of chromosome 17	12	15
t(11;14)	13	18
t(4;14)	16	20
t(14;16)	4	6

Abbreviation: Ig, immunoglobulin.
*Percentage calculated on No. of patients whose fluorescence in situ hybridization analyses were available.

Ninety-two patients (90%) entered the MEL100 phase; five patients died (septic shock, n = 2; pneumonia, n = 2; and pulmonary embolism, n = 1); five patients did not complete the assigned treatment (grade 3 confusion, n = 1; performance status deterioration, n = 1; psychiatric disease unrelated to therapy, n = 1; and insufficient stem-cell harvest, n = 2); one patient withdrew consent; and one patient was lost to follow-up. Eighty-three patients (81%) received tandem MEL100.

Eighty patients entered LP consolidation; six patients did not complete the assigned treatment for toxicity (persistent pancytopenia, n = 4; grade 3 neuropathy, n = 1; and infection, n = 1), and four patients experienced PD (two during consolidation and two during maintenance).

Safety

In this study, eight deaths (8%) as a result of AEs were reported during treatment (three occurred during PAD, and five occurred during MEL100), and seven deaths (7%) were considered treatment related. The most frequent grade 3 to 4 AEs and those with specific clinical relevance are listed in Table 2. Hematologic AEs included neutropenia (n = 87), thrombocytopenia (n = 83), and anemia (n = 13). Nonhematologic AEs included peripheral neuropathy (n = 17), pneumonia (n = 15), fever of unknown origin (n = 13), sepsis (n = 8), constipation (n = 7), thromboembolism (n = 7), and fatigue (n = 7).

During PAD, the most frequent hematologic grade 3 to 4 toxicities were thrombocytopenia (n = 17) and neutropenia (n = 10). G-CSF was required in 12 patients, RBC support was required in six patients, and platelet transfusion was required in three patients. Other common nonhematologic grade 3 to 4 AEs in PAD included peripheral neuropathy (n = 16), pneumonia (n = 10), fatigue (n = 5), and

constipation (n = 5). At the time of analysis, 94% of peripheral neuropathy events had either resolved or decreased by at least one grade. All severe infections occurred in patients with high tumor burden or in poor responders; grade 3 to 4 pneumonia or sepsis was reported in 34% of patients older than 70 years and in 21% of patients younger than 70 years.

During the LP-L consolidation-maintenance phases, the most frequent grade 3 to 4 AEs were neutropenia (n = 13), thrombocytopenia (n = 5), pneumonia (n = 4), and cutaneous rash (n = 3). G-CSF was required in three patients, RBC support was required in one patient, and no platelet transfusions were needed. A delay in the administration of a new treatment cycle was reported in 10 patients, mainly as a result of neutropenia or thrombocytopenia. Two episodes of deep vein thrombosis were reported during the first 4 months of LP consolidation. Dermatologic AEs were typically mild to moderate and were manageable with lenalidomide dose modification and supportive therapy.

Table 2. Adverse Events According to Phase of Therapy

Adverse Event	Grade 3 or 4 Events												PAD/MEL100/LP-L (n = 102)				
	PAD (n = 102)			MEL100 (n = 92)			LP-L (n = 80)			Grade 1 to 2 Events			Grade 3 to 4 Events				
	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)		
Hematologic																	
Neutropenia	10	10	5 to 17	83	90	82 to 95	13	16	9 to 26	ND			87	85	77 to 91		
Thrombocytopenia	17	17	10 to 25	83	90	82 to 95	5	6	2 to 14	ND			83	81	72 to 88		
Anemia	3	3	0 to 8	13	14	8 to 23	0	0	0 to 4	ND			13	13	7 to 21		
Nonhematologic																	
Infection																	
Pneumonia	10	10	5 to 17	5	5	2 to 12	4	5	1 to 12	3	3	0 to 8	15	15	8 to 23		
Fever of unknown origin	3	3	0 to 8	13	14	8 to 23	0	0	0 to 4	10	10	5 to 17	13	13	7 to 21		
Sepsis	3	3	0 to 8	7	8	3 to 15	0	0	0 to 4	0	0	0 to 3	8	8	3 to 13		
Herpes zoster	0	0	0 to 3	0	0	0 to 4	2	2	0 to 9	0	0	0 to 3	2	2	0 to 7		
Hepatitis B reactivation	1	1	0 to 5	0	0	0 to 4	0	0	0 to 4	0	0	0 to 3	1	1	0 to 5		
Gastroenteritis	0	0	0 to 3	0	0	0 to 4	2	2	0 to 9	0	0	0 to 3	2	2	0 to 7		
Neurologic																	
Peripheral neuropathy	16	16	9 to 24	0	0	0 to 4	1	1	0 to 7	37	36	27 to 46	17	17	10 to 25		
CNS toxicity	2	2	0 to 7	0	0	0 to 4	1	1	0 to 7	0	0	0 to 3	3	3	1 to 8		
GI																	
Constipation	5	5	2 to 11	2	2	0 to 8	0	0	0 to 4	16	16	9 to 24	7	7	3 to 14		
Diarrhea	2	2	0 to 7	1	1	0 to 6	0	0	0 to 4	14	14	8 to 22	3	3	1 to 8		
Nausea/vomiting	2	2	0 to 7	4	4	1 to 11	0	0	0 to 4	10	10	5 to 17	6	6	2 to 12		
Mucositis	0	0	0 to 3	3	3	0 to 9	0	0	0 to 4	8	8	3 to 15	3	3	1 to 8		
Intestinal infarction	1	1	0 to 5	0	0	0 to 4	0	0	0 to 4	0	0	0 to 3	1	1	0 to 5		
Thromboembolism																	
Deep vein thrombosis	4	4	1 to 10	0	0	0 to 4	2	2	0 to 9	2	2	0 to 7	6	6	2 to 12		
Pulmonary embolism	1	1	0 to 5	0	0	0 to 4	0	0	0 to 4	0	0	0 to 3	1	1	0 to 5		
Dermatologic																	
Rash	1	1	0 to 5	1	1	0 to 6	3	4	1 to 11	15	15	8 to 23	5	5	2 to 11		
Steven-Johnson syndrome	1	1	0 to 5	0	0	0 to 4	0	0	0 to 4	0	0	0 to 3	1	1	0 to 5		
Other conditions																	
Myocardial infarction	0	0	0 to 3	1	1	0 to 6	0	0	0 to 4	0	0	0 to 3	1	1	0 to 5		
Fatigue	5	5	2 to 11	1	1	0 to 6	1	1	0 to 7	25	24	16 to 34	7	7	3 to 14		
Hyperglycemia	4	4	1 to 10	1	1	0 to 6	0	0	0 to 4	2	2	0 to 7	5	5	2 to 11		
Creatinine increase	1	1	0 to 5	2	2	0 to 8	0	0	0 to 4	3	3	1 to 8	3	3	1 to 8		
Bleeding	2	2	0 to 7	0	0	0 to 4	0	0	0 to 4	5	5	2 to 11	2	2	0 to 7		

NOTE. Grade 1 and 2 adverse events were reported in $\geq 10\%$ of patients; grade 3 and 4 adverse events were reported in $\geq 2\%$ of patients. Other adverse events of particular clinical relevance are also listed. Patients could have more than one adverse event.

Abbreviations: PAD, bortezomib, pegylated liposomal doxorubicin, and dexamethasone; MEL100, melphalan; LP-L, lenalidomide plus prednisone followed by lenalidomide maintenance; ND, not determined.

Table 3. Best Responses to Treatment Endpoints

Best Response	Per-Protocol Population									Intent-to-Treat Population								
	PAD (n = 94)			MEL100 (n = 83)			LP-L (n = 50)			PAD (n = 102)			MEL100 (n = 102)			LP-L (n = 102)		
	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)
CR or VGPR	55	58	48 to 69	68	82	72 to 89	43	86	73 to 94	56	55	45 to 65	78	76	67 to 84	80	78	69 to 86
CR	12	13	6 to 21	32	38	28 to 50	33	66	51 to 79	12	12	6 to 20	34	33	24 to 43	41	40	31 to 50
VGPR	43	46	35 to 56	36	43	32 to 55	10	20	10 to 34	44	43	33 to 53	44	43	33 to 53	39	38	29 to 48
PR	32	34	25 to 44	11	13	7 to 22	5	10	3 to 22	34	33	24 to 43	17	17	10 to 25	15	15	8 to 23
SD	7	8	3 to 15	2	2	0 to 8	2	4	0 to 14	11	11	5 to 18	6	6	2 to 12	6	6	2 to 12
PD	0	0	0 to 4	1	1	0 to 6	0	0	0 to 7	0	0	0 to 3	0	0	0 to 3	0	0	0 to 3
NA	0	0	0 to 4	1	1	0 to 6	0	0	0 to 7	1	1	0 to 5	1	1	0 to 5	1	1	0 to 5

NOTE. Percentage may not total 100% because of rounding.

Abbreviations: PAD, bortezomib, pegylated liposomal doxorubicin, and dexamethasone; MEL100, melphalan; LP-L, lenalidomide plus prednisone followed by lenalidomide maintenance; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available.

Efficacy

In the intent-to-treat analysis, a high proportion of patients achieved immunofixation-negative CR or at least VGPR (Table 3). Median time to partial response (PR) was 21 days (range, 21 to 259 days), and median time to CR was 249 days (range, 63 to 856 days). In the per-protocol analysis, PAD induction resulted in 55 (58%) of 94 patients with at least VGPR, including 12 (13%) of 94 patients with CR; MEL100 ASCT resulted in 68 (82%) of 83 patients with at least VGPR and 32 (38%) of 83 patients with CR; and LP-L consolidation-maintenance resulted in 43 (86%) of 50 patients with at least VGPR and 33 (66%) of 50 patients with CR. Further improvement in response during LP consolidation occurred in eight (16%) of 50 patients (one patient improved from PR to VGPR, one improved from PR to CR, and six improved from VGPR to CR); two (4%) of 50 patients showed improvement in response during lenalidomide maintenance (both from VGPR to CR); 25 of 50 patients were in CR at the beginning of consolidation. The median duration of follow-up from study entry was 21 months (range, 9 to 40 months) for survivors. Progression or relapse occurred in 12 (12%) of 102 patients, and death from any cause occurred in 11 patients (11%). In all patients, the 2-year time to progression rate was 75% (Fig 2A), the 2-year time to next therapy rate was 70%, the 2-year PFS rate was 69% (Fig 2B), and the 2-year OS rate was 86% (Fig 2C).

By exploratory analyses stratified by group, the 2-year PFS rate was 76% in patients with International Staging System (ISS) stage I disease, 67% in patients with stage II disease, and 46% in patients with stage III disease (Fig 3A). The 27 patients with high-risk cytogenetic profiles, including del17, t(4;14), or t(14;16), and the 47 patients with standard cytogenetic profiles had similar PFS ($P = .38$; Fig 3B). This did not change with the inclusion of 24 patients with del13 in the high-risk group ($P = .81$). Patients who achieved CR had a 2-year PFS of 87%, patients who achieved VGPR had a 2-year PFS of 76%, and patients who achieved PR had a 2-year PFS of 43% (Fig 3C). In 26 patients older than 70 years and 76 younger patients, PFS was not significantly different ($P = .16$), although it was slightly prolonged in younger patients.

DISCUSSION

To our knowledge, this is the first phase II study conducted in patients with newly diagnosed MM to date, where a sequential approach including bortezomib as induction and ASCT followed by lenalidomide consolidation-maintenance was explored. In the per-protocol analysis, the immunofixation-negative CR rate was 13% after induction with PAD, which increased to 38% after MEL100, and improved to 66% after LP-L consolidation-maintenance. This suggests that a sequential approach incorporating bortezomib as induction and lenalidomide as consolidation-maintenance improves ORRs after ASCT.

Although results are not univocal, achievement of higher CR or VGPR rates has been associated with a positive impact on OS and clinical benefit.²² Thalidomide, bortezomib, and lenalidomide have been used in combination with dexamethasone and explored as induction before ASCT. They induced a VGPR rate of 25% to 50%.²³⁻²⁵ Higher ORRs have been reported with triple-drug combinations. In our study, responses were rapid; PR or better was already attained after the first cycle of PAD in 69% of patients, and a VGPR rate of 58% was reported at the end of induction. In other studies, bortezomib, thalidomide, and dexamethasone induced a VGPR rate of 61%,²⁶ and bortezomib, lenalidomide, and dexamethasone induced a VGPR rate of 71%.²⁷ The higher VGPR rate and the more prompt response induced by triple combinations including bortezomib are evidence for their use as induction before ASCT. Whether doxorubicin, cyclophosphamide, lenalidomide, or thalidomide should be associated with bortezomib plus dexamethasone remains to be answered.

Both melphalan, prednisone, and thalidomide^{28,29} and bortezomib, melphalan, and prednisone³⁰ are now the standard induction regimens for elderly patients. MEL100 has shown contradictory results. One study showed MEL100 to have similar efficacy as melphalan and prednisone (MP) in patients age 65 to 75 years,²⁹ whereas in another study, MEL100 was superior to melphalan and prednisone in patients age 65 to 70 years.³¹ In our study, patients younger than 70 years showed a slightly better outcome compared with patients older than 70 years, although this was not significant. Although it is difficult to define age limits in an elderly population where the biologic age differs from the anagraphic age, MEL100 is an alternative option for

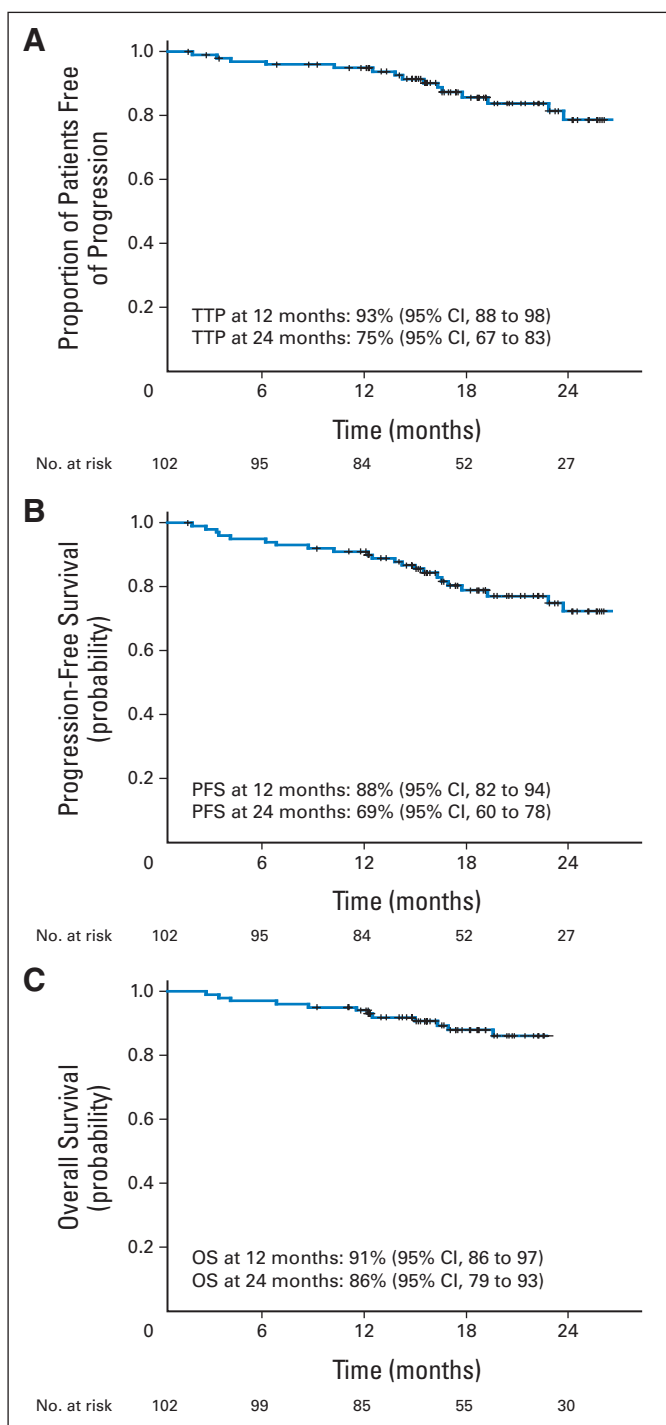


Fig 2. (A) Time to progression, (B) progression-free survival, and (C) overall survival in the intent-to-treat population.

patients tolerating a more intense regimen than conventional treatment or for patients younger than 65 years in whom the presence of comorbidities contraindicates the administration of full-dose ASCT.

The CR rate was 38% after MEL100 and improved to 66% after LP-L consolidation-maintenance, whereas the VGPR rate was almost unchanged. In patients already in VGPR after ASCT, consolidation

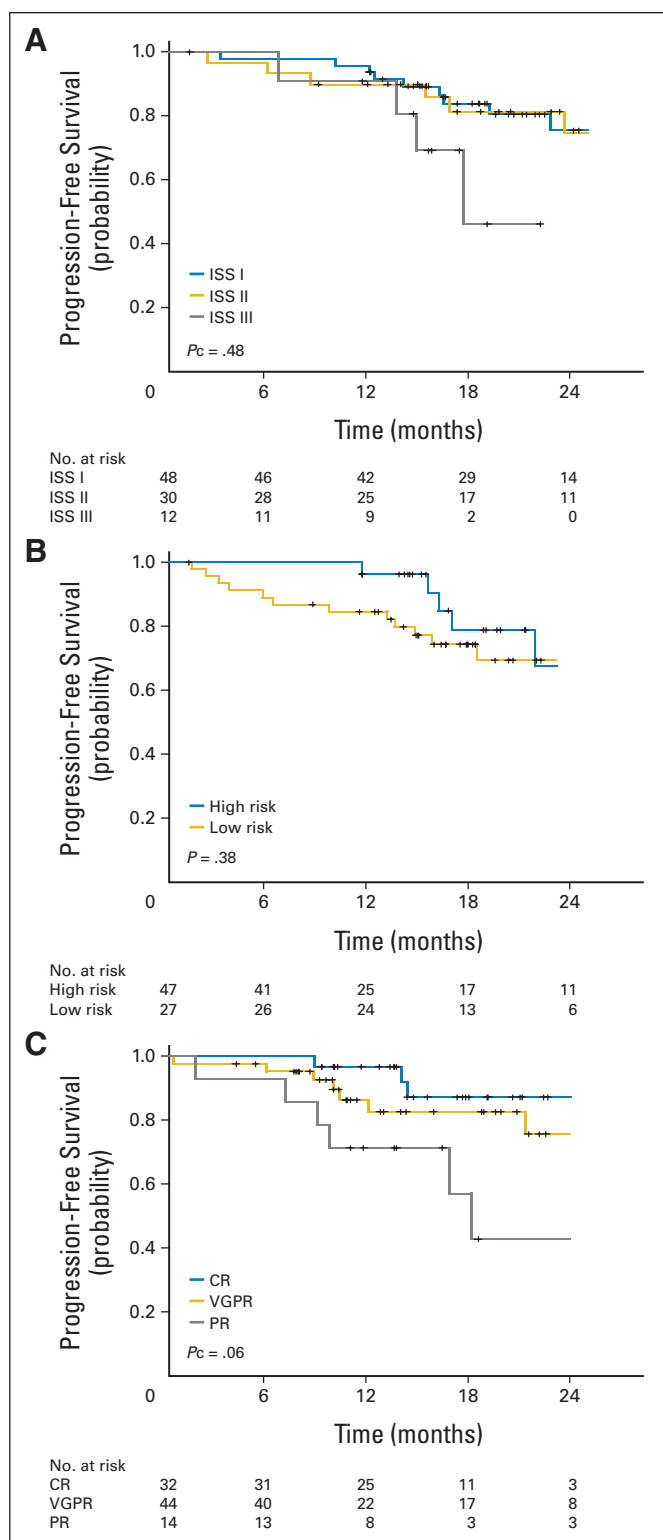


Fig 3. Progression-free survival (PFS) analysis stratified by group. (A) PFS according to patient International Staging System (ISS) stage. (B) PFS according to cytogenetic profile. (C) PFS according to whether patients obtained complete response (CR), very good partial response (VGPR), or partial response (PR; landmark analysis with landmark point at 3 months from the start of therapy). P_c , P value corrected using the Bonferroni correction for multiple comparison.

including bortezomib, thalidomide, and dexamethasone increased the immunofixation-negative CR rate from 23% to 66% and the molecular response rate from 5% to 21%.³² In another study, patients received three courses of bortezomib, cyclophosphamide, and dexamethasone followed by three courses of bortezomib, thalidomide, and dexamethasone with a significant increase in the near-CR rate from 19% after the first three courses to 42% after the last three courses; the VGPR rate was unchanged.³³ In all of these studies, the significant increase in response rates was mainly reported in patients who had achieved VGPR before consolidation. These data show that consolidation with bortezomib and/or immunomodulatory drugs improves ORRs, and this improvement is mainly observed in responsive patients.

In the two phase II studies evaluating efficacy of bortezomib plus melphalan and prednisone³⁴ and lenalidomide plus melphalan and prednisone,³⁵ best responses continued to improve over the treatment course, with approximately 30% of patients achieving maximum M-protein reduction after the first 6 months of therapy. These data support the need of prolonged treatment and support the idea of sequential exposure to different drugs to maximize response depth. Thalidomide alone or in combination with prednisolone has been used as maintenance after ASCT in three independent randomized studies.¹¹⁻¹³ In another randomized study, thalidomide maintenance induced a PFS improvement in patients achieving less than a VGPR with no survival benefit.¹⁴ Both thalidomide and bortezomib can only be used for a limited period of time because of the risk of peripheral neuropathy and are suitable for consolidation. Lenalidomide is a suitable candidate for long-term use without the risk of cumulative toxicity. Ongoing studies are assessing its efficacy as maintenance.

Most AEs were managed with the use of standard approaches. Infections emerged as the most frequent nonhematologic AE, occurring mainly during PAD induction (17%) and MEL100 transplantation (27%). More careful assessment of fevers of unknown origin and prompt institution of antibiotic prophylaxis should reduce their incidence. In an Eastern Cooperative Oncology Group study, use of lower doses of dexamethasone significantly reduced the incidence of infections from 16% to 6%.³⁶ Weekly infusion of dexamethasone may reduce the incidence of infection in the PAD regimen, especially in the elderly. Infections were the cause of six of eight early deaths reported in this study, suggesting a need for a more gentle approach and careful follow-up of frail patients in the first 3 months of therapy after diagnosis and during ASCT.

Grade 3 to 4 peripheral sensory neuropathy was observed in 17 patients. In the Assessment of Proteasome Inhibition for Extending Remission (APEX) and bortezomib, melphalan, and prednisone trials, the incidence of grade 3 neuropathy was 8% and 13%, respectively.^{4,30} In the bortezomib, melphalan, prednisone, and thalidomide trial, the incidence of neuropathy was 6% despite concomitant thalidomide, but bortezomib was administered on a weekly basis.³⁷ These data prompt a modification of the schedule of bortezomib from days 1, 4, 8, and 11 to a less frequent schedule of days 1, 8, 15, and 22 in the elderly. This approach reduces the incidence of peripheral neuropathy by approximately 70% and should be offered to all elderly patients with pre-existing neuropathy.³⁷

Lenalidomide consolidation and maintenance was well tolerated, and the absence of cumulative or persistent neutropenia and/or cu-

mulative thrombocytopenia, together with the absence of peripheral neuropathy, further supports its use as maintenance.

In conclusion, sequential PAD, MEL100, and LP-L is an attractive regimen to maximize the efficacy of ASCT and may represent a new treatment paradigm for patients receiving ASCT. These promising results need further testing in randomized phase III trials and comparison with other attractive induction regimens, such as lenalidomide-based initial therapy. Our findings show high CR rate, prolonged response duration, and good efficacy in all subgroups analyzed, including those with poor prognostic characteristics. These data further support other studies that suggest that bortezomib needs to be administered early in patients with high-risk disease. Randomized studies are needed to assess the role of lenalidomide-containing regimens as maintenance in the treatment of patients with MM undergoing ASCT.

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: None **Consultant or Advisory Role:** Pellegrino Musto, Celgene (C); Mario Boccardo, Celgene (C), Janssen-Cilag (C), Pharmion (C) **Stock Ownership:** None **Honoraria:** Antonio Palumbo, Celgene, Janssen-Cilag; Sara Bringhen, Janssen-Cilag, Celgene; Maria Teresa Petrucci, Janssen-Cilag, Celgene; Pellegrino Musto, Celgene, Janssen-Cilag **Research Funding:** Tommasina Guglielmelli, Celgene, Janssen-Cilag; Nicola Giuliani, Janssen-Cilag; Pellegrino Musto, Celgene; Mario Boccardo, Celgene, Pharmion, Janssen-Cilag **Expert Testimony:** None **Other Remuneration:** None

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Acknowledgment

We thank the patients, Barbara Lupo, MD, statistical staff (Ileana Baldi), data managing staff (Antonella Bono), and nursing staff (Simona Bera and D'Ambrosio Luisella).

Presented in part at the 49th Annual Meeting of the American Society of Hematology, December 7-12, 2007, Atlanta, GA; the 12th Congress of the European Hematology Association, June 7-10, 2007, Vienna, Austria; the 44th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2008, Chicago, IL; and the 50th Annual Meeting of the American Society of Hematology, December 6-9, 2008, San Francisco, CA.