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Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma

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ABSTRACT

BACKGROUND

Lenalidomide has tumoricidal and immunomodulatory activity against multiple myeloma. This double-blind, multicenter, randomized study compared melphalan–prednisone–lenalidomide induction followed by lenalidomide maintenance (MPR-R) with melphalan–prednisone–lenalidomide (MPR) or melphalan–prednisone (MP) followed by placebo in patients 65 years of age or older with newly diagnosed multiple myeloma.

METHODS

We randomly assigned patients who were ineligible for transplantation to receive MPR-R (nine 4-week cycles of MPR followed by lenalidomide maintenance therapy until a relapse or disease progression occurred [152 patients]) or to receive MPR (153 patients) or MP (154 patients) without maintenance therapy. The primary end point was progression-free survival.

RESULTS

The median follow-up period was 30 months. The median progression-free survival was significantly longer with MPR-R (31 months) than with MPR (14 months; hazard ratio, 0.49; P<0.001) or MP (13 months; hazard ratio, 0.40; P<0.001). Response rates were superior with MPR-R and MPR (77% and 68%, respectively, vs. 50% with MP; P<0.001 and P=0.002, respectively, for the comparison with MP). The progression-free survival benefit associated with MPR-R was noted in patients 65 to 75 years of age but not in those older than 75 years of age (P=0.001 for treatment-by-age interaction). After induction therapy, a landmark analysis showed a 66% reduction in the rate of progression with MPR-R (hazard ratio for the comparison with MPR, 0.34; P<0.001) that was age-independent. During induction therapy, the most frequent adverse events were hematologic; grade 4 neutropenia was reported in 35%, 32%, and 8% of the patients in the MPR-R, MPR, and MP groups, respectively. The 3-year rate of second primary tumors was 7% with MPR-R, 7% with MPR, and 3% with MP.

CONCLUSIONS

MPR-R significantly prolonged progression-free survival in patients with newly diagnosed multiple myeloma who were ineligible for transplantation, with the greatest benefit observed in patients 65 to 75 years of age. (Funded by Celgene; MM-015 ClinicalTrials.gov number, NCT00405756.)

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Melphalan–prednisone (MP) has long been the treatment of choice for patients with multiple myeloma who are older than 65 years of age.[1] The introduction of new agents in the past few years has substantially changed the treatment of multiple myeloma. MP plus either thalidomide or bortezomib is reported to improve progression-free survival and overall survival, as compared with MP alone,[2,3] and these combinations are now considered the new standards of care for elderly patients with newly diagnosed multiple myeloma who are ineligible for stem-cell transplantation.[1]

Lenalidomide in combination with dexamethasone is effective in relapsed or refractory multiple myeloma[4-6] and in newly diagnosed multiple myeloma.[7,8] Maintenance therapy with lenalidomide after autologous stem-cell transplantation improves median progression-free survival or time to progression by at least 50%.[9,10] In this phase 3, multicenter, randomized, double-blind, placebo-controlled trial, we evaluated the efficacy and safety of induction therapy with melphalan–prednisone–lenalidomide (MPR) followed by lenalidomide maintenance therapy (MPR-R), as compared with MPR or MP without maintenance therapy, in patients with newly diagnosed multiple myeloma who were ineligible for transplantation.

Methods

Patients

Patients with symptomatic, measurable, newly diagnosed multiple myeloma who were not candidates for transplantation (≥65 years of age) were eligible for this trial. Exclusion criteria were an absolute neutrophil count of less than 1500 per cubic millimeter, a platelet count of less than 75,000 per cubic millimeter, a hemoglobin level of less than 8.0 g per deciliter, renal insufficiency (a serum creatinine level of >2.5 mg per deciliter [>221 μmol per liter]), and peripheral neuropathy of grade 2 or higher. All patients gave written informed consent. The study was approved by the institutional review boards of the participating centers and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Study Design and Oversight

The study, conducted at 82 centers in Europe, Australia, and Israel, recruited patients from February 2007 through September 2008. Patients were randomly assigned (in a 1:1:1 ratio) to receive oral MPR-R (152 patients), MPR (153 patients), or MP (154 patients) and were stratified according to age (65 to 75 years vs. >75 years) and International Staging System stage (stage I or II vs. stage III, with higher stages indicating more severe disease); the staging criteria are described in the Supplementary Appendix (available with the full text of this article at NEJM.org). Patients and treating physicians were unaware of the treatment assignments. The maximum tolerated doses of lenalidomide and melphalan in combination were established in a preceding phase 1 and 2 study.[11]

The trial was designed by the academic authors in collaboration with Celgene. Employees of the company assisted with the study design, data collection, data analysis, and writing of the manuscript in collaboration with the senior academic authors. The first draft of the manuscript was developed by the first author. All authors had full access to all the data on study unblinding and had final responsibility for the decision to submit the manuscript for publication. Medical writers from Excerpta Medica and MediTech Media provided assistance with the writing of the manuscript, which was funded by Celgene. All authors were fully responsible for all content and editorial decisions for this manuscript and vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol. The full study protocol and statistical analysis plan are available at NEJM.org.

Study Treatments

The MPR-R regimen consisted of induction with nine 28-day cycles of melphalan (at a dose of 0.18 mg per kilogram of body weight on days 1 through 4), prednisone (2 mg per kilogram on days 1 through 4), and lenalidomide (10 mg on days 1 through 21), followed by lenalidomide maintenance (10 mg on days 1 through 21 of each 28-day cycle) until disease progression or the development of unacceptable rates of adverse effects. The MPR group received the same MPR induction, followed by placebo maintenance, and the MP group received MP induction (at the same doses and on the same schedule as the MPR regimen), with placebo during induction and maintenance. Patients in whom progressive disease developed during induction therapy discontinued the double-blind treatment phase and could enroll in an open-label

extension phase to receive lenalidomide (25 mg on days 1 through 21 of each 28-day cycle) alone or with dexamethasone (40 mg on days 1 through 4, 9 through 12, and 17 through 20).

All patients received aspirin thromboprophylaxis (75 to 100 mg daily) during induction; thromboprophylaxis could be continued during maintenance at the treating physician's discretion. Dose reductions were allowed as specified by the protocol and are described in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival. The primary comparison was between MPR-R and MP. A 50% improvement in progression-free survival was considered to be clinically relevant. This study was not designed or powered to assess overall survival. Secondary end points included overall survival, response rate, time to response, duration of response, response quality, and adverse events.

Responses to treatment and disease progression were assessed with the use of the European Group for Blood and Marrow Transplantation criteria,[12] and a very good partial response was defined according to the International Uniform Response Criteria for Multiple Myeloma (both sets of criteria are described in the Supplementary Appendix).[13] Serum and 24-hour urine samples were collected at baseline and every 28 days for 3 years and every 56 days thereafter until completion of the double-blind phase of the trial. Laboratory assessments of efficacy were performed centrally; treatment response and disease progression were adjudicated by a panel of independent experts. Progression-free survival was calculated from the time of randomization until the date of progression or death from any cause during treatment or until data censoring at the last date at which the patient was known to be progression-free. Overall survival was calculated from the time of randomization until the date of death from any cause or until data censoring at the last date at which the patient was known to be alive. Bone marrow samples for cytogenetic analysis were collected, when possible, and analyzed by the central cytogenetic laboratory (Hannover, Germany) with the use of fluorescence in situ hybridization (FISH) (probes supplied by Abbott). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[14]

STATISTICAL ANALYSIS

We estimated that 450 patients (150 per treatment group) would need to be enrolled for the study to have a statistical power of 80% to detect a 50% improvement in median progression-free survival, from 15 months (MP) to 22.5 months (MPR-R). The efficacy analysis was performed on an intention-to-treat basis for all efficacy end points. The safety analysis included patients who received at least one dose of the assigned study treatment. Response data were compared with the use of the chi-square test. Time-to-event data were analyzed with the Kaplan–Meier method, and treatment groups were compared with the use of the log-rank test. The Cox proportional-hazards model was used to estimate hazard ratios and 95% confidence intervals. Subgroup analyses of progression-free survival were performed on the basis of stratification factors (age [65 to 75 years vs. >75 years] and International Staging System stage [stage I or II vs. stage III]) and relevant baseline characteristics. A landmark analysis (MPR-R vs. MPR) that included all patients who started lenalidomide maintenance therapy was performed to define the contribution of maintenance therapy to progression-free survival. The risk of a second primary tumor was compared with the risk of disease progression or death (risk–benefit assessment) by assessing the Kaplan–Meier curves for second primary tumors and disease progression or death for each treatment group. In addition, an analysis of event-free survival, with a second primary tumor considered to be an event, was performed to test the robustness of the primary analysis of progression-free survival.

Three analyses were specified by the protocol, when 148 progression-free survival events (50%), 207 events (70%), and 296 events (100%) had occurred. On the basis of the first analysis (data cutoff, April 2009), the data and safety monitoring committee recommended unblinding of the study because the prespecified O'Brien–Fleming superiority boundary (two-sided alpha level of 0.003 at 50% information [148 progression-free survival events]) for the primary end point had been crossed (hazard ratio, 0.50; $P<0.001$). The data at the first study site were unblinded on May 11, 2010, at approximately 76% of progression-free survival events, and data on centrally adjudicated response and progression-free survival available up to this date are presented here. Data on overall survival and safety are the latest available (data cutoff, February 28, 2011).

RESULTS

PATIENTS AND TREATMENT

A total of 459 patients were randomly assigned to receive MPR-R (152 patients), MPR (153 patients), or MP (154 patients). Approximately two thirds of the patients completed induction treatment (Fig. 1). Baseline characteristics were well balanced among the treatment groups (Table 1), except for a higher Karnofsky performance-status score in the MP group than in the MPR-R and MPR groups. The median age was 71 years; 111 patients (24%) were older than 75 years of age. A high proportion of patients had International Staging System stage III disease (48 to 51% in the three treatment groups). The median duration of follow-up was 30 months (range, 1 to 47).

EFFICACY

Progression-free survival was the primary end point. MPR-R significantly prolonged progression-free survival (median, 31 months) as compared with MPR (median, 14 months; hazard ratio, 0.49; P<0.001) and MP (median, 13 months; hazard ratio, 0.40; P<0.001); the MPR and MP groups did not differ significantly with respect to progression-free survival (Fig. 2A).

In a prespecified landmark analysis, lenalidomide maintenance significantly extended progression-free survival from the start of maintenance therapy (median, 26 months) as compared with placebo (median, 7 months; hazard ratio for the MPR-R group as compared with the MPR group, 0.34; P<0.001) (Fig. 2B, and Table 1 in the Supplementary Appendix).

The progression-free survival benefit associated with MPR-R was consistent across all subgroups of patients defined by stratification factors and baseline characteristics, except those older than 75 years of age (Fig. 1 in the Supplementary Appendix). Heterogeneity of treatment effects between the age subgroups was confirmed by a significant treatment-by-age interaction (P=0.001). Among patients 65 to 75 years of age, MPR-R significantly prolonged progression-free survival (median, 31 months), as compared with MPR (median, 15 months; hazard ratio, 0.48; P<0.001) and MP (median, 12 months; hazard ratio, 0.30; P<0.001). In this age group, MPR also improved progression-free survival as compared with MP (hazard ratio, 0.62; P=0.006). In patients older than 75 years of age, median progression-free survival was 19 months with MPR-R, 12 months with MPR, and 15 months with MP.

A very good partial response or better (secondary end point) was reported in 50 patients (33%) in the MPR-R group, 50 (33%) in the MPR group, and 19 (12%) in the MP group (Table 2). The median time to the first evidence of a response was 2 months with MPR-R and MPR and 3 months with MP (P<0.001 for both comparisons with MP). The median duration of a complete or partial response was longer with MPR-R (29 months) than with MPR (13 months) or MP (13 months) (P<0.001 for both comparisons [MPR-R with MPR, and MPR-R with MP]).

Death occurred in 43 patients (28%) in the MPR-R group, 52 (34%) in the MPR group, and 45 (29%) in the MP group. The 3-year overall survival rate (secondary end point) was 70% with MPR-R, 62% with MPR, and 66% with MP (Fig. 2C). Data on salvage therapy and post-progression survival are shown in Table 2 in the Supplementary Appendix.

SAFETY

During induction, the most frequent adverse events were hematologic; hematologic adverse events occurred more often in the lenalidomide groups than in the MP group. Grade 4 neutropenia was reported in 52 patients (35%) in the MPR-R group, 49 (32%) in the MPR group, and 12 (8%) in the MP group; grade 4 thrombocytopenia occurred in 17 patients (11%), 19 patients (12%), and 6 patients (4%), respectively (Table 3). Granulocyte colony-stimulating factor was administered in 100 patients (67%) in the MPR-R group, 87 (57%) in the MPR group, and 46 (30%) in the MP group and did not increase the risk of infection; platelet transfusions were performed in 8 patients (5%), 6 patients (4%), and 4 patients (3%), respectively. The incidence of febrile neutropenia did not exceed 5% in any treatment group; there were no bleeding events. In the lenalidomide groups, the most frequent and clinically relevant nonhematologic adverse events were infections (Table 3). Grade 3 or 4 deep-vein thrombosis occurred in 3% of patients in the lenalidomide groups and 1% of those in the MP group. Adverse events caused drug discontinuation in 16% of patients in the MPR-R group, 14% of those in the MPR group, and 5% of those in the MP group.

During the maintenance phase of MPR-R, the incidence of new or worsened grade 3 or 4 adverse

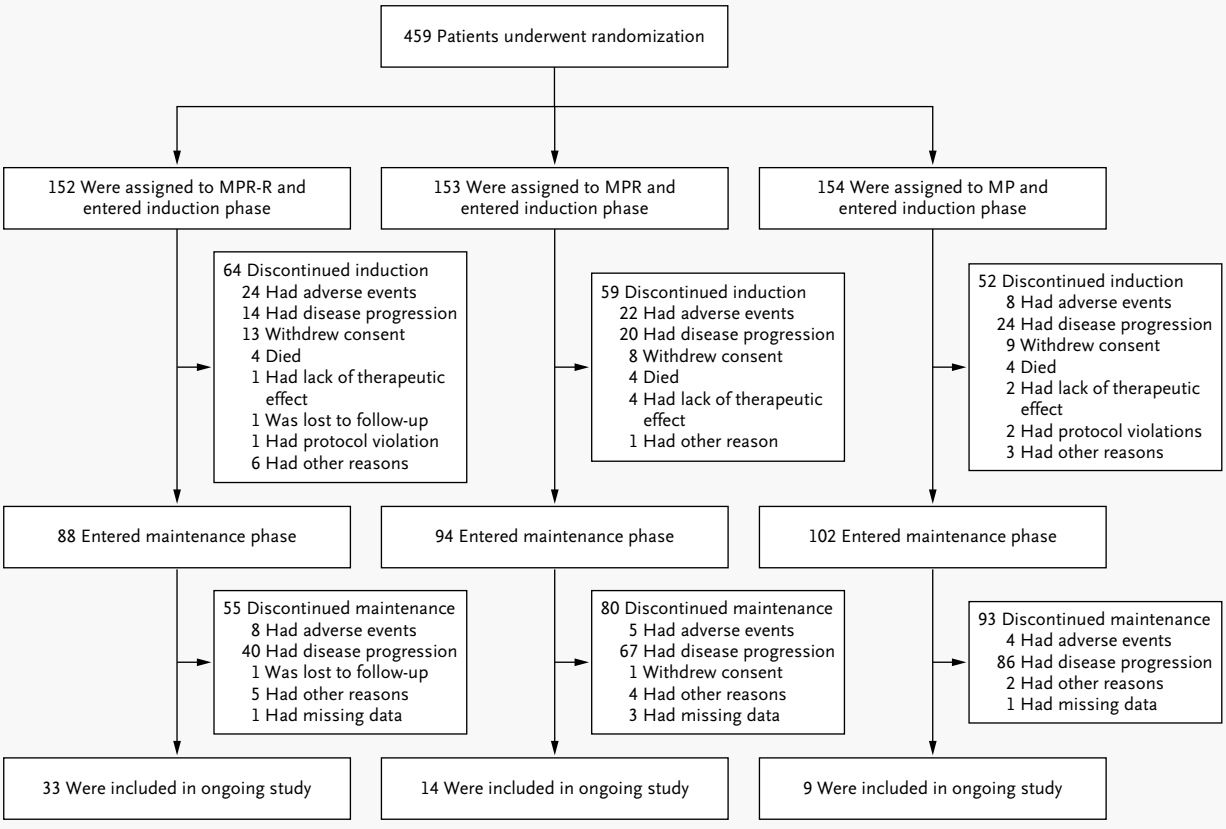


Figure 1. Randomization and Follow-up of the Study Patients.

MP denotes melphalan–prednisone induction followed by placebo maintenance, MPR melphalan–prednisone–lenalidomide induction followed by placebo maintenance, and MPR-R melphalan–prednisone–lenalidomide induction followed by lenalidomide maintenance.

events was low (0 to 6%) (Table 3). Grade 4 neutropenia and thrombocytopenia were reported in 2 patients (2%) and 5 patients (6%), respectively. Granulocyte colony-stimulating factor was administered in 27 patients (31%) during lenalidomide maintenance therapy; 1 (1%) received platelet transfusions. There were no reports of grade 3 or 4 febrile neutropenia or bleeding during maintenance therapy. Deep-vein thrombosis was reported in 2 patients (2%) in the MPR-R group and 1 (1%) in the MPR group; 8% of patients discontinued lenalidomide maintenance because of adverse events.

The 3-year rate of invasive second primary tumors was 7% with MPR-R, 7% with MPR, and 3% with MP. The 3-year rate of progression or death was higher, at 58%, 91%, and 94%, respectively (Fig. 2 in the Supplementary Appendix). The analysis of event-free survival, with a second primary tumor considered to be an event, was consistent with the primary analysis of progression-free survival ($P<0.001$) (Fig. 3 in the Supplementary Appendix). Hematologic second primary tumors included acute myeloid leukemia (in four patients in the MPR-R group and two in the MPR group), myelodysplastic syndromes (in one in the MPR-R group, three in the MPR group, and one in the MP group), T-cell acute lymphoblastic leukemia (in one in the MPR-R group), and chronic myelomonocytic leukemia (in one in the MPR-R group). Solid tumors of heterogeneous types occurred with similar frequency in all treatment groups (in five patients in the MPR-R group, four in the MPR group, and three in the MP group).

Four deaths in the MPR-R and MPR groups were considered to be related to lenalidomide: 3 deaths among the 152 patients (2%) in the MPR-R group (which were due to pneumonia,

Table 1. Demographic and Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	MPR-R (N=152)	MPR (N=153)	MP (N=154)
Age			
Median — yr	71	71	72
Range — yr	65–87	65–86	65–91
65–75 yr — no. (%)	116 (76.3)	116 (75.8)	116 (75.3)
>75 yr — no. (%)	36 (23.7)	37 (24.2)	38 (24.7)
Sex — no. (%)			
Male	71 (46.7)	82 (53.6)	75 (48.7)
Female	81 (53.3)	71 (46.4)	79 (51.3)
Karnofsky performance status score†			
Median	80‡	80	90
Range	60–100	60–100	60–100
International Staging System stage — no. (%)§			
I	28 (18.4)	32 (20.9)	28 (18.2)
II	50 (32.9)	47 (30.7)	48 (31.2)
III	74 (48.7)	74 (48.4)	78 (50.6)
Lytic bone lesions — no. (%)			
Present	108 (71.1)	110 (71.9)	101 (65.6)
Absent	43 (28.3)	40 (26.1)	51 (33.1)
Missing data or not determined	1 (0.7)	3 (2.0)	2 (1.3)
Creatinine clearance — no. (%)			
≥60 ml/min	72 (47.4)	83 (54.2)	77 (50.0)
<60 ml/min	78 (51.3)	69 (45.1)	76 (49.4)
Missing data	2 (1.3)	1 (0.7)	1 (0.6)
Cytogenetic features — no. (%)			
Adverse			
Deletion 17p	6 (3.9)	6 (3.9)	7 (4.5)
Translocation (4;14)	6 (3.9)	2 (1.3)	3 (1.9)
Translocation (14;16)	0	1 (0.7)	0
Favorable¶	14 (9.2)	19 (12.4)	13 (8.4)
Deletion 13q	38 (25.0)	45 (29.4)	38 (24.7)
Normal‖	1 (0.7)	4 (2.6)	2 (1.3)
Could not be evaluated	61 (40.1)	61 (39.9)	59 (38.3)
Missing data	32 (21.1)	21 (13.7)	41 (26.6)

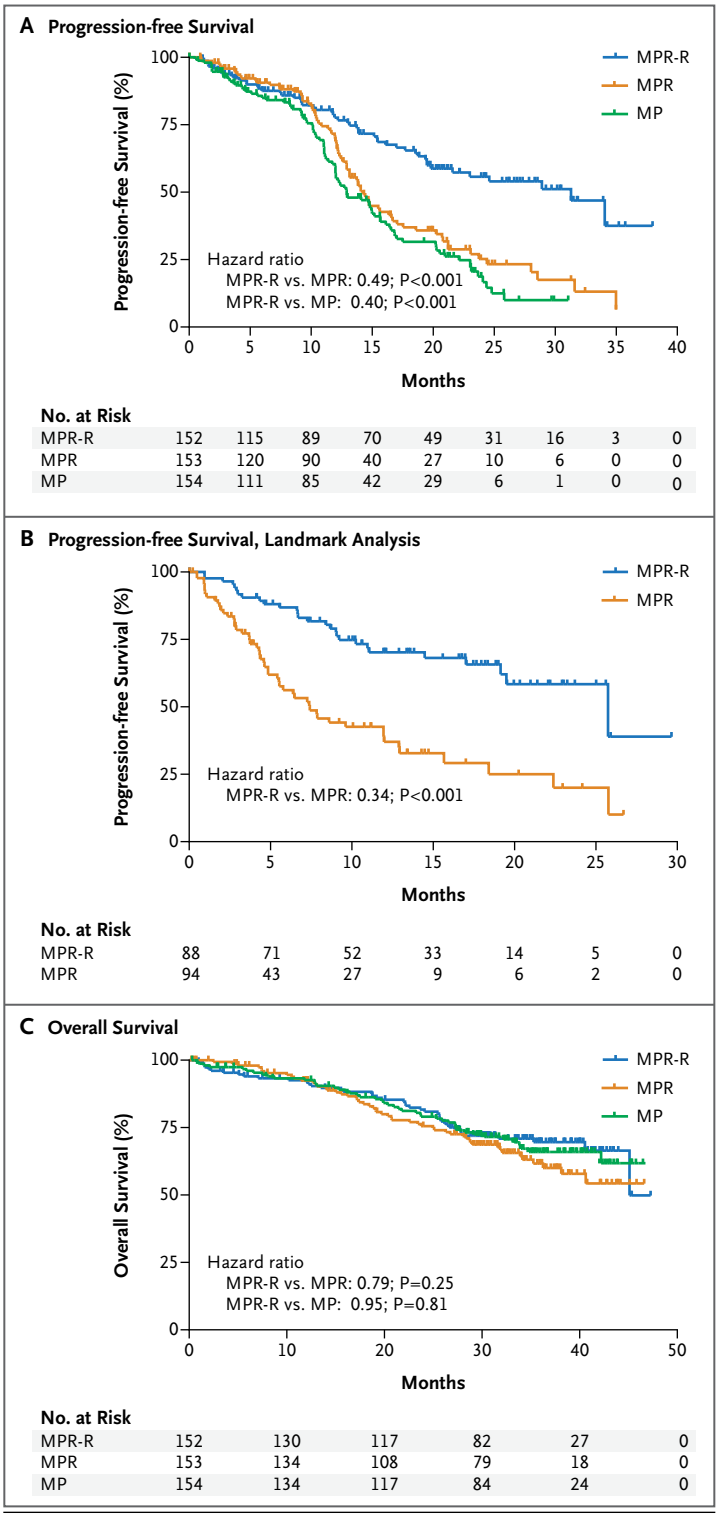
* MP denotes melphalan–prednisone induction followed by placebo maintenance, MPR melphalan–prednisone–lenalidomide induction followed by placebo maintenance, and MPR-R melphalan–prednisone–lenalidomide induction followed by lenalidomide maintenance.
† Scores on the Karnofsky performance status scale range from 0 to 100, with higher scores indicating better performance status.
‡ P=0.03 for the comparison with the MP group.
§ Higher stages indicate more severe disease.
¶ A favorable prognosis was defined as the presence of a hyperdiploid karyotype and translocation t(11;14)(p13;q32).
‖ Normal karyotype was defined by normal signal constellations on fluorescence in situ hybridization (FISH).

septic shock, and cardiogenic shock) and 1 death among the 153 patients (0.7%) in the MPR group (due to lobar pneumonia).

In the MPR-R and MPR groups, the lenalidomide dose was reduced during induction in 90 of 230 patients (39%) who were 65 to 75 years of age, as compared with a dose reduction in 38 of 72 patients (53%) who were older than 75 years of age; the melphalan dose was reduced in 79 (34%) and 32 (44%) of these patients, respectively. Thirty pa-

Figure 2. Survival Outcomes in the Intention-to-Treat Population.

Panel A shows the Kaplan–Meier estimates of median progression-free survival (MPR-R group, 31 months; MPR group, 14 months; and MP group, 13 months). Panel B shows the effect of maintenance therapy on progression-free survival from the start of maintenance in patients who had received MPR induction therapy (landmark analysis; median progression-free survival from maintenance initiation, 26 months in the MPR-R group and 7 months in the MPR group). Panel C shows the median overall survival among all patients (MPR-R group, 45.2 months; MPR group, not reached; and MP group, not reached).



tients (13%) who were 65 to 75 years of age and 16 patients (22%) who were older than 75 years of age discontinued treatment because of adverse events (Table 3 in the Supplementary Appendix). Thus, patients 65 to 75 years of age received 85% of the planned dose intensity of lenalidomide during MPR induction, as compared with 74% among those older than 75 years of age (Table 3 in the Supplementary Appendix). Time-dependent Cox regression analysis showed a positive relationship between progression-free survival and the cumulative dose of either melphalan (MPR-R group, $P<0.001$; MPR group, $P=0.02$) or lenalidomide (MPR-R and MPR groups, $P<0.001$), indicating an effect of treatment tolerance on efficacy.

DISCUSSION

This phase 3 study showed that MPR-R, a three-drug induction regimen followed by lenalidomide maintenance, was more effective than MPR or MP with placebo maintenance and was associated with a reduced rate of progression by 51% and 60%, respectively, in patients with newly diagnosed multiple myeloma who were ineligible for transplantation. MPR induction followed by placebo was superior to MP in patients 65 to 75 years of age but not in those older than 75 years of age. Lenalidomide maintenance therapy was associated with acceptable adverse-event rates and improved progression-free survival regardless of age.

The median progression-free survival of 31 months with MPR-R compares favorably with bortezomib–melphalan–prednisone (22 months)[15] and melphalan–prednisone–thalidomide (20 months).[2] Although cross-trial comparisons are difficult, our study showed a median progression-free survival advantage of 18 months (MPR-R vs. MP), as compared with 7 months with the fixed-duration regimen of bortezomib–melphalan–prednisone versus MP[15] and 5 months with melphalan–prednisone–thalidomide versus MP.[2]

MPR as an induction regimen was superior to MP in the speed of response, overall response rate,

Table 2. Best Response among Patients in the Intention-to-Treat Population during Double-Blind Treatment.*

Variable	MPR-R (N=152)	MPR (N=153)	MP (N=154)
Best response			
Complete or partial response — no. (%)	117 (77.0)†	104 (68.0)‡	77 (50.0)
Complete response	15 (9.9)	5 (3.3)	5 (3.2)
Partial response§	102 (67.1)	99 (64.7)	72 (46.8)
Very good partial response¶	35 (23.0)	45 (29.4)	14 (9.1)
Stable disease — no. (%)	28 (18.4)	40 (26.1)	70 (45.5)
Progressive disease — no. (%)	0	2 (1.3)	0
Response could not be evaluated — no. (%)	7 (4.6)	7 (4.6)	7 (4.5)
Time to event			
Time to first evidence of response — mo			
Median	2†	2†	3
Range	1–9	1–6	1–15
Duration of response — mo			
Complete or partial response			
Median	29‖	13	13
95% CI	22–NR	12–15	10–18
Complete response			
Median	NR‖	31	22
95% CI	36–NR	23–33	10–24
Partial response§			
Median	19	11	10
95% CI	11–NR	9–13	9–15
Very good partial response¶			
Median	28†	15	18
95% CI	22–NR	13–22	10–22

* NR denotes not reached.
† P<0.001 for the comparison with the MP group.
‡ P=0.002 for the comparison with the MP group.
§ A partial response was defined as a 50 to 99% reduction in serum and urinary levels of myeloma protein.
¶ A very good partial response was defined as a 90 to 99% reduction in serum and urinary levels of myeloma protein.
‖ P<0.001 for the comparison with the MPR group and the comparison with the MP group.

and response quality and, for patients 65 to 75 years of age, provided a significant progression-free survival benefit. MPR did not improve progression-free survival, as compared with MP, in patients older than 75 years of age. The lack of efficacy in this age group may be due to an increased rate of adverse events associated with MPR and the need for more frequent dose modifications in older patients than in younger patients.

In the present study, the major influence on progression-free survival was associated with lenalidomide maintenance therapy. A landmark analysis showed that lenalidomide maintenance reduced the rate of progression among all patients, regardless of age, by 66% as compared with placebo. The median progression-free survival was 31 months with MPR-R. Similarly, the median progression-free survival was 31 months with bortezomib–melphalan–prednisone or bortezomib–thalidomide–prednisone induction followed by maintenance with bortezomib–thalidomide or bortezomib–prednisone[16] and 37 months with a four-drug regimen, bortezomib–melphalan–prednisone–thalidomide, followed by maintenance with bortezomib–thalidomide.[17] Altogether, these results confirm the benefits of maintenance therapy with respect to progression-free survival. The influence on overall survival remains unclear.

Table 3. Grade 3 and 4 Adverse Events Occurring in at Least 5% of the Safety Population and Adverse Events of Clinical Interest Occurring in at Least 2% of the Safety Population.

Event	MPR-R (N=150)		MPR (N=152)		MP (N=153)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Induction therapy						
Hematologic adverse events — no. (%)						
Neutropenia	100 (67)	52 (35)	97 (64)	49 (32)	45 (29)	12 (8)
Thrombocytopenia	53 (35)	17 (11)	58 (38)	19 (12)	18 (12)	6 (4)
Anemia	36 (24)	4 (3)	40 (26)	4 (3)	21 (14)	2 (1)
Leukopenia	35 (23)	6 (4)	39 (26)	8 (5)	21 (14)	2 (1)
Febrile neutropenia	7 (5)	3 (2)	2 (1)	2 (1)	0	0
Nonhematologic adverse events — no. (%)						
Infection*	14 (9)	1 (1)	20 (13)	3 (2)	11 (7)	0
Fatigue	8 (5)	0	2 (1)	1 (1)	5 (3)	0
Deep-vein thrombosis	2 (1)	0	6 (4)	1 (1)	1 (1)	0
Cardiac disorder†	5 (3)	3 (2)	4 (3)	4 (3)	5 (3)	0
Diarrhea	3 (2)	1 (1)	2 (1)	0	0	0
Rash‡	7 (5)	0	7 (5)	0	2 (1)	0
Maintenance therapy						
Hematologic adverse events— no./total no. (%)						
Neutropenia	4/88 (5)	2/88 (2)	0/94	0/94	1/102 (1)	0/102
Thrombocytopenia	0/88	5/88 (6)	0/94	2/94 (2)	2/102 (2)	0/102
Anemia	2/88 (2)	2/88 (2)	2/94 (2)	1/94 (1)	5/102 (5)	0/102
Nonhematologic adverse events— no./total no. (%)						
Infection*	3/88 (3)	2/88 (2)	2/94 (2)	0/94	1/102 (1)	2/102 (2)
Fatigue	2/88 (2)	1/88 (1)	0/94	0/94	1/102 (1)	0/102
Deep-vein thrombosis	2/88 (2)	0/88	1/94 (1)	0/94	0/102	0/102
Diarrhea	3/88 (3)	1/88 (1)	0/94	0/94	0/102	0/102
Bone pain	4/88 (5)	0/88	1/94 (1)	0/94	4/102 (4)	1/102 (1)
Diabetes mellitus	2/88 (2)	0/88	0/94	0/94	0/102	0/102

* Infection was described in the following terms: pneumonia, lower respiratory tract infection, upper respiratory tract infection, bronchitis, sepsis, urinary tract infection, diverticulitis, herpes zoster, infective arthritis, bacteriuria, cellulitis, gastrointestinal tract infection, oral infection, tooth infection, septic shock, appendicitis, sinusitis, postprocedural infection, streptococcal bacteremia, *Escherichia coli* infection, and meningitis.

† Cardiac disorders included atrial fibrillation, angina pectoris, cardiac failure, coronary artery disease, left or right ventricular failure, myocardial ischemia, palpitations, tachycardia, acute coronary syndromes, acute myocardial infarction, first-degree atrioventricular block, and tachyarrhythmia.

‡ Rash was described in the following terms: rash, pruritus, drug eruption, erythema, and papular rash.

After a median follow-up of 30 months, the number of deaths was low (31% event rate), with no significant differences among the groups. The 3-year overall survival rate with MPR-R (70%) compared well with that of melphalan–prednisone–thalidomide (53%)[2] and bortezomib–melphalan–prednisone (68%).[15] The study included a relatively high proportion of patients with a poor prognosis; the frequency of International Staging System stage III was 48 to 51% across the groups. This proportion was 18 to 38% across melphalan–prednisone–thalidomide trials and 35% with bortezomib–melphalan–prednisone.[2,3] In the current study, the overall survival analysis was probably confounded by the crossover of patients with disease progression to open-label treatment with lenalidomide–dexamethasone. Longer follow-up is required to evaluate an overall survival benefit.

The most frequently reported adverse events were hematologic. Grade 4 neutropenia occurred in 35% of the patients in the MPR-R group during induction. Neutropenia from MPR-R was managed with granulocyte colony-stimulating factor, with no increased risk of infections. The rate of nonhematologic adverse events, including deep-vein thrombosis, with MPR-R was low. The rate of discontinuation due to adverse events in the MPR-R group was 16%, which is lower than the rate with melphalan–prednisone–thalidomide (33 to 45%)[18-21] and similar to the rate with bortezomib–melphalan–prednisone (12 to 34%).[3,15,17] Lenalidomide maintenance was associated with little evidence of cumulative toxic effects. Clinical trials are needed to determine an appropriate duration of maintenance therapy.

The 3-year risk of an invasive second primary tumor was 7% with MPR-R and 3% with MP. The increased risk of a second primary tumor with lenalidomide is mainly confined to acute myeloid leukemia or myelodysplastic syndromes and is observed when lenalidomide is given with or after melphalan.[9,10,22] The leukemogenic potential of all alkylating agents, which is usually observed after 3 to 5 years of follow-up, is well established.[23-25] The interaction between lenalidomide and melphalan may increase the leukemogenic risk. The benefits of MPR-R appear to outweigh the risk of a second primary tumor; longer follow-up and larger samples of patients are needed to confirm this judgment.

In conclusion, MPR-R is an effective treatment for patients with newly diagnosed multiple myeloma who are ineligible for transplantation. Although MPR is active in patients 65 to 75 years of age, its benefits are less evident in older patients. However, lenalidomide maintenance extends progression-free survival regardless of age.

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APPENDIX

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