Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed multiple myeloma patients aged 65 years or older: results of a randomized phase III trial

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ABSTRACT

The MM-015 trial assessed the effect of lenalidomide-based therapy on health-related quality of life. Patients (n=459) with newly diagnosed multiple myeloma aged 65 years or over were randomized 1:1:1 to nine 4-week cycles of lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance; or lenalidomide, melphalan, and prednisone, or melphalan and prednisone, with no maintenance therapy. Patients completed health-related quality of life questionnaires at baseline, after every third treatment cycle, and at treatment end. Health-related quality of life improved in all treatment groups during induction therapy. Patients receiving lenalidomide maintenance had the most pronounced improvements, Global Health Status/Quality of Life (P<0.05), Physical Functioning (P<0.01), and Side Effects of Treatment (P<0.05) out of 6 pre-selected health-related quality of life domains. More patients receiving lenalidomide maintenance achieved minimal important differences (P<0.05 for Physical Functioning). Therefore, lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in patients with newly diagnosed multiple myeloma. (*Clinicaltrials.gov identifier NCT00405756).*

Introduction

The introduction of efficacious agents like thalidomide, lenalidomide, and bortezomib in the treatment of multiple myeloma (MM) has placed greater importance on health-related quality of life (HRQoL) as an outcome measure[1-7] and a factor that influences treatment decisions.[8-11] In the randomized phase III MM-015 trial of patients with newly diagnosed MM (NDMM) aged 65 years or over, median progression-free survival (PFS) was significantly longer with the combination of melphalan, prednisone, and lenalidomide, followed by lenalidomide maintenance therapy (MPR-R; 31 months) than with MPR or MP without maintenance therapy (14 and 13 months, respectively; P<0.0001 for both).[12] A pre-defined secondary end point of the MM-015 trial was HRQoL. The primary goal of this analysis was to compare HRQoL outcomes in the MPR-R and MP groups. Because the PFS benefit with MPR-R was observed primarily in the subset of patients aged 65-75 years,[12,13] HRQoL outcomes in this subset were also assessed.

Design and Methods

MM-015 is a prospective, multicenter, phase III, randomized, double-blind, placebo-controlled, 3-arm parallel group study. Full study details are provided elsewhere.[12] Briefly, patients were randomized (1:1:1) to one of 3 treatment arms, which involved nine 28-day cycles of; i) MPR followed by maintenance therapy with lenalidomide (MPR-R); ii) MPR followed by maintenance therapy with placebo, MPR); iii) MP plus placebo followed by maintenance therapy with placebo (MP) (*Online Supplementary Figure S1*). Patients receive maintenance therapy until: i) progressive disease (PD); ii) discontinuation for reasons other than PD (DC); iii) all patients are followed for at least five years from randomization or until death. The study was conducted in compliance with the Independent Review Board/Independent Ethics Committee procedures, the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and local regulations governing the conduct of clinical studies. Written informed consent was obtained from all patients before enrollment.

Two European Organization for Research and Treatment of Cancer (EORTC) HRQoL questionnaires were used: the generic 30-item EORTC QLQ-C30,[14] and the 20-item MM-specific module EORTC QLQ-MY20.[15] Each questionnaire takes approximately 10-15 min to complete.[16] The QLQ-C30 includes 5 functional domains (Physical Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning, and Role Functioning), where a higher score indicates better function. For the 9 symptom domains (Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties), lower scores indicate fewer symptoms. The QLQ-C30 also contains an item on overall Global Health Status/QoL (subsequently referred to as Global QoL), where a higher score indicates better quality of life. The QLQ-MY20 includes 2 functional domains (Future Perspective and Body Image) and 2 symptom domains (Disease Symptoms and Side Effects of Treatment). Higher scores indicate better function and more symptoms, respectively. At the time this study was initiated, the 24-item

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QLQ-MY24 was in development, and 4 questions regarding social support were removed during validation, resulting in the validated QLQ-MY20.[15] For consistency, the QLQ-MY24 form was administered throughout this study, but the 4 questions removed during validation were omitted from the analysis.

Questionnaires were completed at baseline; after every third treatment cycle (i.e. before starting cycles 4, 7, 10, 13, 16, etc.); and at the time of treatment discontinuation due to PD or DC. Follow-up included HRQoL assessment every 6 months (168 days) during the open-label extension phase. Six HRQoL domains were selected *a priori* for analysis based on their perceived clinical relevance: Global QoL, Physical Functioning, Fatigue, and Pain from QLQ-C30, and Disease Symptoms, and Side Effects of Treatment from QLQ-MY20. Domain scores were calculated if responses were given to at least 50% of items in that particular domain.[17] Compliance rates with HRQoL reporting were calculated for each time point across treatment groups. Mixed models were used to estimate the treatment effect on HRQoL over time, adjusted and unadjusted for baseline HRQoL scores (*Online Supplementary Methods*).

The minimal important difference (MID) was calculated to help identify clinically meaningful changes in HRQoL scores from baseline, irrespective of whether they were of statistical significance.[18,19] Domain-specific MIDs of the 6 pre-selected domains were identified by calculating the standard error of measurement (SEM).[20,21] Positive MIDs denote improvements for the HRQoL domains Global QoL and Physical Functioning; negative values denote improvements in Pain, Fatigue, Disease Symptoms, and Side Effects of Treatment.

Cumulative distribution frequency (CDF) graphs were also plotted for each of the 6 pre-selected HRQoL domains at cycles 10 and 16 (*Online Supplementary Methods*).

Statistical methodology is described in the *Online Supplementary Methods*.

Results and Discussion

From February 2007 to September 2008, 459 patients were enrolled at 82 treatment centers and randomized to MPR-R (n=152), MPR (n=153), or MP (n=154). Patient demographics and disease-related characteristics are described in the *Online Supplemental Results*. Compliance rates were generally high (>76% across assessment time points considered and >65% at PD/DC) and consistent across treatment groups (*Online Supplemental Results*).

Health-related quality of life scores during induction therapy

At baseline, patients randomized to MPR-R had worse HRQoL scores than those assigned to MPR or MP (Table 1), but the difference was statistically significant only for Physical Functioning (P=0.014). Longitudinal HRQoL data for all patients are shown in Figure 1. During induction, mean Global QoL scores increased (i.e. improved) by 12.2 in MPR-R (P<0.001) and 6.2 in MP (P<0.05), and mean Physical Functioning scores increased (i.e. improved) by 9.0 in MPR-R (P<0.001) and 5.1 in MP (P<0.01). Mean Fatigue scores decreased (i.e. improved) by 7.5 in MPR-R (P<0.01) and 6.9 in MP (P<0.01), as did mean Pain scores (-17.2 for MPR-R and -9.8 for MP; both P<0.001) and Disease Symptoms scores (-7.9 for MPR-R, P<0.001; and -5.4 for MP, P<0.01) (Table 1). Scores for Side Effects of Treatment showed minimal changes from baseline in both MPR-R (-1.6) and MP patients (+0.3), and both changes were not significant. The improvement in HRQoL from baseline in MPR-R patients aged 65-75 years was slightly greater than that for all MPR-R patients (*Online Supplementary Results* and *Figure S2*). Comparable changes in HRQoL scores could not be replicated in the smaller subgroup of patients aged over 75 years.

Health-related quality of life scores during maintenance therapy

Improvements in HRQoL observed during MPR induction were maintained in patients receiving lenalidomide maintenance therapy (Table 1). In the MPR-R group, statistically significant improvements were seen at cycle 16 compared with baseline for all domains, except Side Effects of Treatment. Statistically significant improvements were not consistently observed for MPR and MP patients.

Analyses of both induction and maintenance therapy

Results of the mixed-model analyses indicated a significant difference in changes in Physical Functioning scores across treatment groups: scores improved significantly (P<0.05) from baseline in MPR-R and MPR patients but worsened in MP patients (interaction term P=0.004) (*Online Supplementary Figure S3*). Scores in the other domains showed the same pattern: scores improved (the slope was positive and significant for Global QoL [P<0.05] and negative for the symptom domains Side Effects of Treatment [P<0.05], Fatigue and Pain) in the MPR-R arm and worsened (the slope was negative for Global QoL and positive for Fatigue, Pain and Disease Symptoms) in the MP arm (*Online Supplementary Figure S3*). Where slopes were equal in sign between MPR-R and MP (Disease Symptoms and Side Effects of Treatment) HRQoL changes were more favorable for MPR-R patients. The results were similar after adjustment for baseline HRQoL scores, patient and disease characteristics, with Physical Functioning scores significantly improving (positive slope) in both MPR (P<0.05) and MPR-R (P<0.01) patients, and both patient groups improving significantly more than MP patients (both P<0.01), whose scores worsened. While there was no statistically significant group difference in Global QoL scores (P=0.11 for MPR-R *vs.* MP), MPR-R patients reported significant improvement (P<0.05) with a positive slope coefficient. MPR-R patients also reported a significant improvement (negative slope coefficient) in Side Effects of Treatment (P<0.05) (*Online Supplementary Figure S4*). Across the other HRQoL domains, HRQoL with MPR-R improved in seven of the thirteen domains (QLQ-C30 Role Functioning, Emotional Functioning, Social Functioning, Nausea/Vomiting, Appetite Loss, Constipation, and QLQ-MY20 Future Perspectives). QLQ-C30 Cognitive Functioning, Dypsnea and Insomnia worsened for both MPR-R and MP, but less so in the MPR-R group. In the 3 remaining domains (QLQ-C30 Diarrhea, Financial Difficulties, and QLQ-MY20 Body Image), HRQoL worsened for MPR-R and improved for MP, but differences between MPR-R and MP were only statistically significant for Diarrhea (P<0.05). Similarly, other than Diarrhea (P<0.05), none of the slopes for the six HRQoL scores showing a worsening trend for MPR-R were statistically significantly different from zero, this is equivalent to a stabilization in HRQoL.

Minimal important differences

Observed MIDs for each HRQoL domain and the assessment time points at which patients in each arm on average

achieved the MID are presented in Table 2. MID values ranged from an absolute value of 6 (Side Effects of Treatment) to an absolute value of 12 (Pain). Over time, clinically meaningful improvements in HRQoL, as determined by the MID, were more frequently observed in patients receiving MPR-R than those receiving MPR or MP.

Table 1. HRQoL mean (SD) domain scores by study arm during the induction and maintenance phases (including within-group changes from baseline and cycle 10) by (A) EORTC QLQ-C30 and (B) EORTC QLQ-MY20 questionnaires.

A

Study arm	BL	Induction Cycle 4	Induction Cycle 7	Cycle 10	Cycle 10 vs. BL	Cycle 13	Maintenance Cycle 16	Cycle 16 vs. 10	Cycle 16 vs. BL
QLQ-C30 Global QoL									
MPR-R (N=152)	49.6(23.5) n=137	54.2(20.2) n=122	61.3(19.3) n=103	63.7(18.0) n=90	+12.2(25.4)*** n=83	61.6(20.1) n=74	62.2(17.1) n=64	-4.1(14.9)* n=61	+11.3(25.1)** n=60
MPR (N=153)	53.2(23.5) n=142	58.4(20.5) n=128	58.9(22.6) n=117	61.4(22.7) n=91	+8.8(24.7)*** n=86	61.8(21.3) n=76	63.3(18.4) n=54	+0.4(16.8) n=46	+7.0(26.5) n=49
MP (N=154)	52.8(22.8) n=147	58.5(20.1) n=132	58.0(19.4) n=116	61.5(18.3) n=100	+6.2(24.6)* n=96	60.5(19.0) n=84	61.9(18.9) n=65	+1.0(17.0) n=60	+8.1(25.1) n=62
QLQ-C30 Physical Functioning									
MPR-R (N=152)	57.5(25.3) n=140	61.6(23.6) n=126	66.3(22.2) n=106	68.6(20.7) n=91	+9.0(22.9)*** n=87	71.3(20.0) n=77	72.6(20.3) n=65	+0.3(11.7) n=62	+10.2(25.2)** n=63
MPR (N=153)	64.0(24.3) n=146	67.4(22.3) n=132	71.0(20.4) n=118	71.0(22.8) n=99	+8.5(25.6)*** n=95	72.2(22.2) n=78	73.2(17.3) n=56	+1.9(15.2) n=50	+7.6(22.7)* n=53
MP (N=154)	65.5(23.8) n=148	70.4(21.9) n=136	69.1(23.0) n=117	72.2(19.2) n=99	+5.1(20.4)** n=96	69.8(21.1) n=84	67.6(20.2) n=65	−2.0(13.3) n=60	+1.1(19.3) n=63
QLQ-C30 Fatigue									
MPR-R (N=152)	49.3(25.6) n=140	43.6(24.2) n=126	39.7(23.2) n=105	39.4(23.3) n=91	−7.5(27.3)** n=87	36.8(21.8) n=76	35.2(22.4) n=65	+0.5(15.6) n=61	−10.1(27.0)* n=63
MPR (N=153)	44.2(27.1) n=146	38.8(24.2) n=132	34.2(23.4) n=118	36.3(26.1) n=99	−7.6(29.8)*** n=95	33.5(22.7) n=78	31.3(20.4) n=55	−3.0(15.9) n=50	−9.7(28.8) n=53
MP (N=154)	42.6(27.4) n=147	37.2(22.7) n=136	35.9(20.7) n=116	33.3(22.0) n=99	−6.9(28.3)** n=95	33.0(20.5) n=84	37.3(21.8) n=65	+3.3(18.2) n=59	−4.1(26.3)* n=62
QLQ-C30 Pain									
MPR-R (N=152)	48.8(34.8) n=140	31.9(27.7) n=126	30.5(27.0) n=105	31.7(27.0) n=92	−17.2(34.8)*** n=88	31.4(28.3) n=76	28.0(24.5) n=65	−1.6(18.5) n=62	−21.4(33.0)*** n=63
MPR (N=153)	44.9(30.2) n=146	31.4(27.7) n=132	28.4(26.7) n=118	28.1(29.3) n=99	−15.6(35.3)*** n=95	31.0(24.7) n=78	33.6(22.8) n=55	+4.6(24.3) n=50	−11.0(33.0)* n=53
MP (N=154)	43.5(33.0) n=148	31.2(28.8) n=135	31.1(28.4) n=118	31.2(27.1) n=100	−9.8(31.7)*** n=97	30.6(24.9) n=84	31.3(25.4) n=65	+0.6(24.0) n=60	−12.2(30.0)** n=63

B

Study arm	BL	Induction Cycle 4	Induction Cycle 7	Cycle 10	Cycle 10 vs. BL	Cycle 13	Maintenance Cycle 16	Cycle 16 vs. 10	Cycle 16 vs. BL
QLQ-MY20 Disease Symptoms									
MPR-R (N=152)	34.0(23.6) n=138	23.3(18.4) n=122	22.7(17.8) n=102	25.6(18.9) n=91	−7.9(23.0)*** n=85	24.8(20.5) n=75	23.7(20.4) n=65	−0.9(14.7) n=61	−11.4(23.2)** n=61
MPR (N=153)	32.1(21.5) n=142	24.3(19.3) n=128	22.8(19.2) n=118	24.4(19.7) n=97	−7.1(23.9)*** n=91	24.9(17.9) n=78	26.7(18.5) n=55	+1.4(16.1) n=49	−5.9(25.8) n=51
MP (N=154)	32.3(22.4) n=148	26.9(21.4) n=133	26.1(20.2) n=127	26.2(19.4) n=98	−5.4(18.8)** n=95	26.9(20.2) n=83	29.4(19.8) n=64	+2.2(16.0) n=57	−3.4(20.7) n=62
QLQ-MY20 Side Effects of Treatment									
MPR-R (N=152)	20.6(15.0) n=138	20.9(13.2) n=122	19.8(13.7) n=101	18.7(15.2) n=91	−1.6(14.5) n=85	14.9(13.7) n=75	17.8(12.9) n=65	+0.9(8.3) n=61	−2.6(14.5) n=61
MPR (N=153)	19.0(15.8) n=141	19.1(15.1) n=128	17.6(16.5) n=118	17.4(16.8) n=96	0.0(16.0) n=89	16.4(13.3) n=78	15.4(14.5) n=55	−2.9(11.7) n=48	−2.9(14.2) n=50
MP (N=154)	17.1(14.4) n=147	17.8(14.1) n=132	17.9(12.3) n=116	16.0(14.3) n=98	+0.3(12.6) n=94	15.7(12.8) n=83	16.0(12.5) n=64	+0.6(11.8) n=57	−0.9(12.2) n=61

*The P value is calculated based on a paired t-test (within-group mean change): *P<0.05; **P<0.01; ***P<0.001. HRQoL observations at PD/DC, if occurring earlier than cycle 16 were carried forward to the next measurement time point. BL: baseline; MP: melphalan and prednisone; MPR: melphalan, prednisone, and lenalidomide; MPR-R: melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance therapy.*

Achievement of the MID was observed as early as cycle 4 for Pain; at cycle 16, the MID was reached in 5 of the 6 domains in patients receiving MPR-R, but in only 2 of the 6 domains in patients receiving MP. Changes in HRQoL scores from baseline to cycles 10 and 16, as depicted in CDF graphs, generally favored MPR-R over MP, both overall and in the subset of patients aged 65-75 years (*Online Supplementary Figures S5* and *S6*) as also indicated by the percentages of patients achieving the MID in each treatment arm (*Online Supplementary Figure S7*).

Discussion

In this analysis, statistically significant improvements in HRQoL from baseline were observed in all treatment arms (MPR-R, MPR, and MP) for all HRQoL domains assessed, except QLQ-MY20 Side Effects of Treatment. Improvements in HRQoL score from baseline were generally greater in patients who received lenalidomide, and the difference was statistically significant for QLQ-C30 Physical Functioning (MPR-R *vs.* MP). Clinically meaningful improvements in HRQoL from baseline were more frequently observed in patients who received MPR-R than those who received MP. The results therefore provide evidence of a favorable effect of MPR-R over MP in terms of Physical Functioning, and a clear trend in improvements in all other HRQoL domains tested, including Global QoL, Fatigue, Pain, and Disease Symptoms. The statistically non-significant change in Side Effects of Treatment scores from baseline in the MPR-R group and its comparability with scores in the MP group highlights the favorable tolerability profile of the MPR-R regimen, both during induction and maintenance.

Table 2. Observed MIDs from baseline.

HRQoL domain score (range 0–100)	Baseline scores: Mean	SD	Internal consistency[1]	SEM	MID[2]	Assessment time points (cycle) with patients on average achieving MID[3]: MPR-R	MPR	MP
Global QoL	51.9	23.3	0.917	6.71	+7	7, 10, 13, 16	7, 10, 13	16
Physical Functioning	62.4	24.4	0.862	9.06	+9	10, 13, 16	13	None observed
Fatigue	45.3	26.8	0.867	9.77	–10	16	13	None observed
Pain	45.7	32.7	0.874	11.61	–12	4, 7, 10, 13, 16	4, 7, 10, 13	4, 13, 16
Disease Symptoms	32.8	22.5	0.791	10.29	–10	16	None observed	None observed
Side Effects of Treatment	18.8	15.1	0.845	5.94	–6	None observed	None observed	None observed

[1]Cronbach's alpha. [2]Thresholds for clinically meaningful score changes from baseline are based on domain-specific distribution based methods (1 SEM). Positive values denote improvements for Global Quality of Life and Physical Functioning. Negative values denote improvements for Pain, Fatigue, Disease Symptoms and Side Effects of Treatment. [3]Data from patients who discontinued from the study prior to cycle 16 were carried forward to the next planned measurement time point in analysis. HRQoL: health-related quality of life; MID: minimal important difference; MP: melphalan and prednisone; MPR: melphalan, prednisone, and lenalidomide; MPR-R: melphalan, prednisone, and lenalidomide, followed by lenalidomide maintenance therapy; SEM: standard error of measurement; SD: standard deviation.

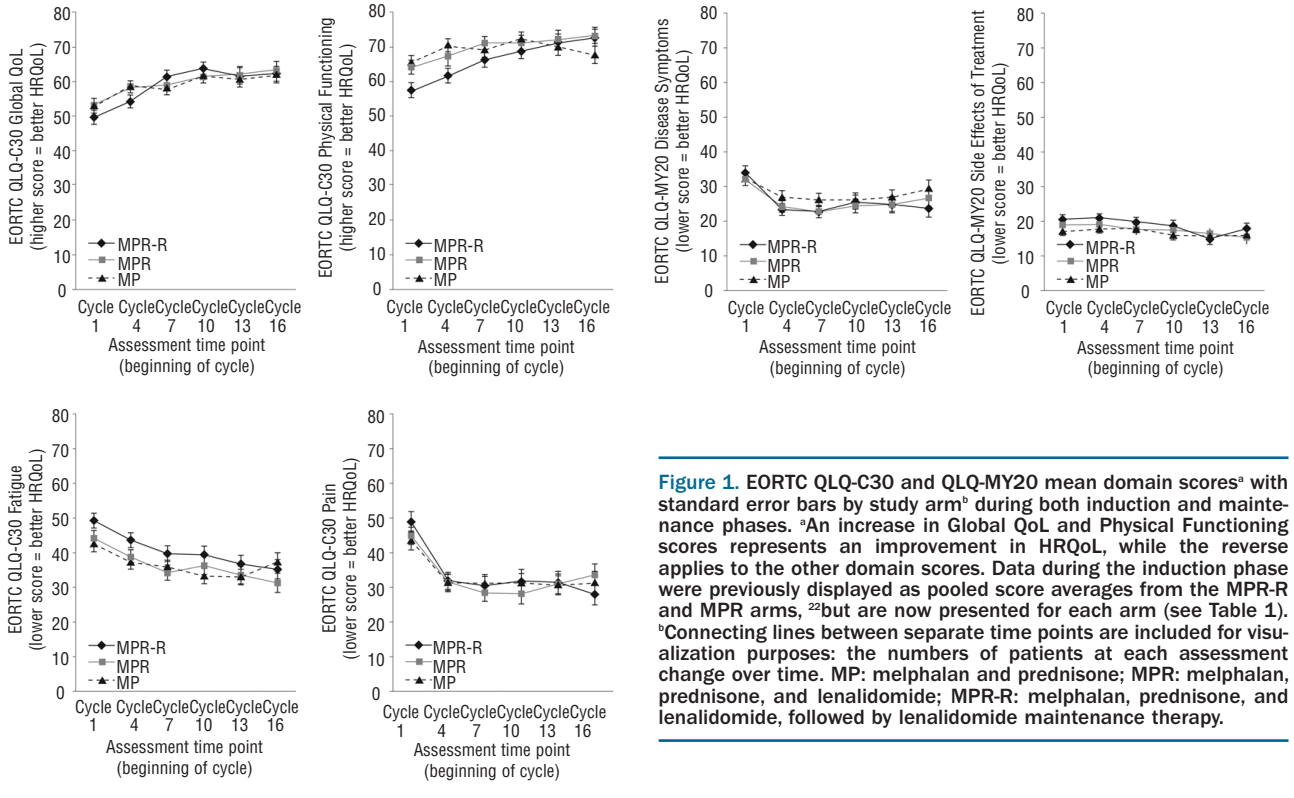

Figure 1. EORTC QLQ-C30 and QLQ-MY20 mean domain scores[a] with standard error bars by study arm[b] during both induction and maintenance phases. [a]An increase in Global QoL and Physical Functioning scores represents an improvement in HRQoL, while the reverse applies to the other domain scores. Data during the induction phase were previously displayed as pooled score averages from the MPR-R and MPR arms, [22]but are now presented for each arm (see Table 1). [b]Connecting lines between separate time points are included for visualization purposes: the numbers of patients at each assessment change over time. MP: melphalan and prednisone; MPR: melphalan, prednisone, and lenalidomide; MPR-R: melphalan, prednisone, and lenalidomide, followed by lenalidomide maintenance therapy.

The results observed in patients aged 65-75 years were consistent with findings from the overall study population. It is possible that observed improvements in HRQoL could be a cumulative effect of the withdrawal of more severely ill patients with poorer HRQoL. However, use of the mixed-model repeated measures analysis across time points helped to ensure that any observed changes were not attributable primarily to the changing nature of the sample over time. The comparable findings among the MPR-R, MPR, and MP groups in terms of patient and disease characteristics as well as HRQoL compliance rates further suggest balanced HRQoL findings across treatment arms. The MID estimates for QLQ-C30 ranged from 6 to 12 points, consistent with previously reported MIDs[23] (*Online Supplementary Information*).

These findings differ from those of the VISTA trial, which evaluated the addition of bortezomib to MP (VMP) in transplant-ineligible patients with NDMM.[24] Since in the VISTA trial, HRQoL scores worsened during the first 4 cycles of VMP therapy compared with baseline and with MP, further studies are needed directly to compare the HRQoL impact of novel anti-myeloma treatment regimens.

In summary, NDMM patients treated with MPR-R report steady improvements in HRQoL during therapy, including a significantly greater improvement in Physical Functioning compared with patients treated with MP. Results were comparable and slightly more favorable in patients aged 65-75 years. These findings, taken together with the primary results of the MM-015 trial, demonstrate that MPR-R is a safe and effective treatment option for patients with NDMM that may lead to improved HRQoL.

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