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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Supplementary Appendix

Design and Methods

Compliance

A patient was considered compliant at a particular time point if at least 50% of all items (i.e. over the whole questionnaire) were completed. Compliance rates per time point and for each HRQoL instrument were calculated as the number of compliant patients divided by the number of patients with clinical data at that assessment. Compliance rates at each assessment were compared among treatment arms, with representativeness assessed by comparing baseline characteristics of patients who were compliant against those who dropped out and those who were non-compliant either because they returned no HRQoL data, or completed less than 50% of HRQoL items.

Cumulative distribution frequency (CDF) graphs

CDF graphs were plotted for each of the 6 pre-selected HRQoL domains at cycles 10 and 16. For example, for cycle 10 and for each EORTC domain of interest, each patient's HRQoL score change from baseline was plotted on the x-axis. The x-axis is oriented so that the furthest value on the left represents the greatest improvement in functioning/symptom domain scores. The cumulative percentage of patients achieving each documented HRQoL score improvement between baseline and cycle 10 was plotted on the y-axis. Each CDF, therefore, plots a continuum of HRQoL changes and the percentage of patients experiencing these changes. The CDF graph increases from 0% and data from the patient who experienced the greatest improvement in HRQoL from baseline to cycle 10, through to 100% and data from the last patient in rank order who experienced the largest deterioration of HRQoL between baseline and cycle 10. Results were plotted for all 3 treatment arms. For each HRQoL domain, a vertical line was drawn in each graph at the point score change from baseline equivalent to the MID. As a result, the percentage of patients achieving the MID for individual treatment arms can
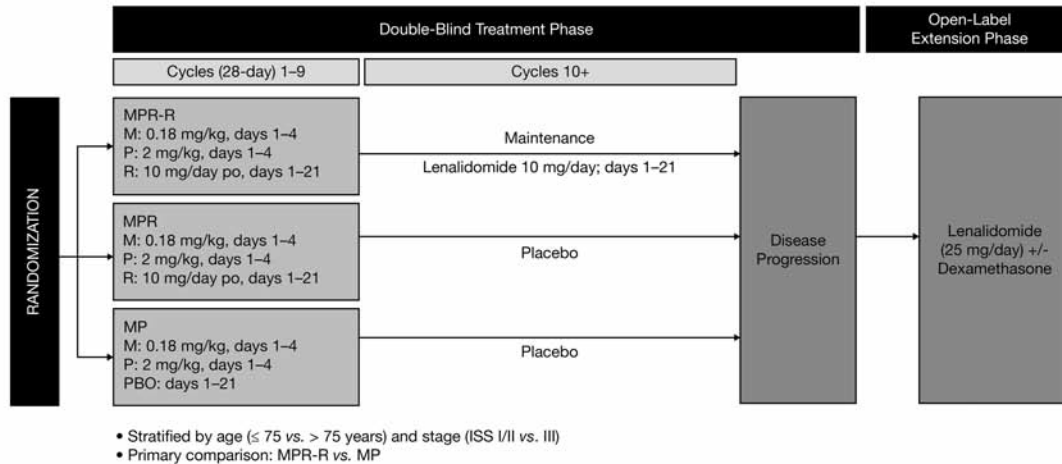
be read off the y-axis at the vertical line intercept with each individual CDF. The percentage of patients achieving the MID at an individual measurement time point (i.e. cycle 10 and 16, each measured against HRQoL at baseline) depicts only one of a continuum of HRQoL point changes as illustrated by the CDFs.

Statistical analysis

Statistical analyses were conducted on the intention-to-treat population based on the date on which the first study site was unblinded (May 11, 2010). All analyses were performed using SAS® version 9.1 or higher (SAS Institute Inc., Cary, NC, USA). Continuous data are presented as mean with SD. Analyses were conducted up to the cycle at which each study arm had 30 or more participants at the time the study was unblinded (cycle 16). HRQoL reported at PD or DC was carried forward to the next time point for observations occurring prior to cycle 16. Differences between paired measurements (e.g. HRQoL scores at baseline, cycle 10, and cycle 16) and categorical measurements (percentages of patients meeting the MID) were assessed using paired t-tests and χ^2-tests, respectively.

To estimate the treatment effect on HRQoL scores over time, a random intercept/slope model (using PROC MIXED in SAS) was used to estimate the slope (i.e. the change in HRQoL scores over time) for each treatment group and compare slopes between treatment groups (i.e. the treatment-group-by-time interaction), with intercept and time as random effects. Unadjusted models included treatment group, time from baseline (in months), and treatment-group-by-time interaction. Adjusted models included all variables from the unadjusted model plus baseline HRQoL score, age, gender, ISS stage, baseline beta-2 microglobulin, baseline renal function, and baseline plasma cell percentage as further control variables. To be included in the analysis, subjects had to have a non-missing baseline HRQoL score, at least one non-missing post-baseline score, and for the adjusted models, non-missing baseline clinical and demographic data.

A

- Stratified by age (≤ 75 *vs.* > 75 years) and stage (ISS I/II *vs.* III)
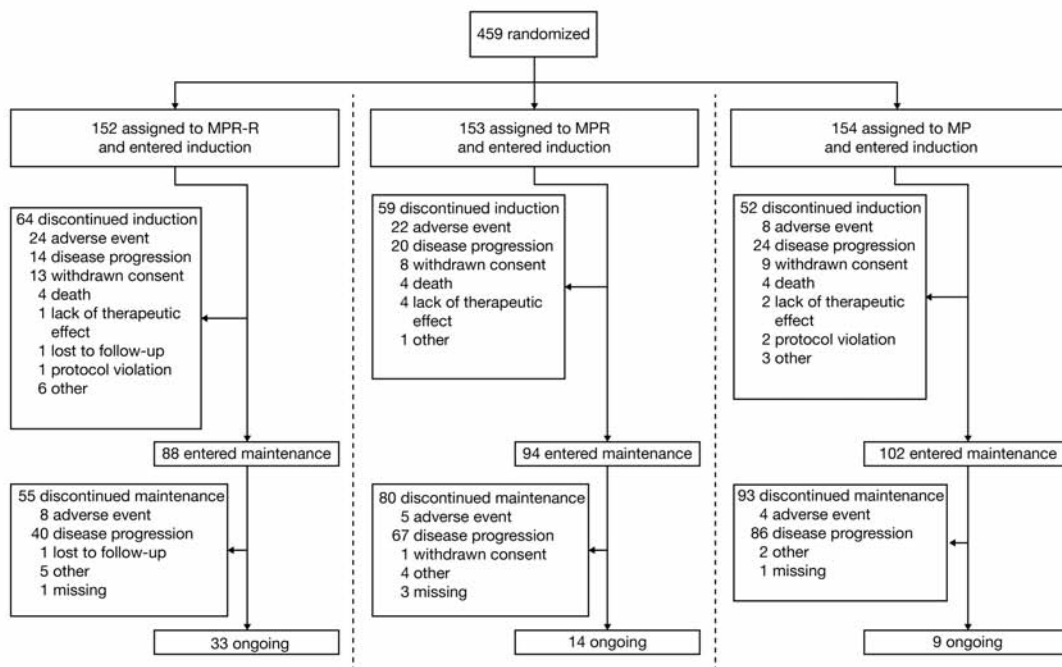- Primary comparison: MPR-R *vs.* MP

B

Figure S1. MM-015 study design and patient recruitment. (A) Study design overview. (B) CONSORT diagram for MM-015 patients (May 11, 2010 data cut off). ISS: International Scoring System.

Results

Patients' characteristics

A total of 459 patients were enrolled at 82 treatment centers and randomized to MPR-R (n=152), MPR (n=153), or MP (n=154). Approximately 60% of patients in each treatment arm entered the maintenance-therapy phase of treatment. Demographics and disease-related characteristics were generally balanced among the treatment groups. Mean (SD) age (years) was 71.9 (5.3), 72.1 (5.2), 72.0 (5.3) in patients treated with MPR-R, MPR, and MP, respectively. The percentage of patients aged over 75 years was similar across treatment groups (23.7%, 24.2%, and 24.7%, respectively), as was the proportion of female patients (53.3%, 48.4%, and 51.3%, respectively). Approximately half of the patients in each arm had International Staging System (ISS) stage III disease (47.7%, 48.4%, 50.6%, respectively). Across the MPR-R, MPR, and MP groups, respectively, mean (SD) plasma cell percentages were 39.8 (24.8), 39.3 (25.0), 37.9 (23.7); mean (SD) beta-2 microglobulin was 6.4 (3.7), 6.7 (4.1), 6.3 (3.7) mg/L, and mean
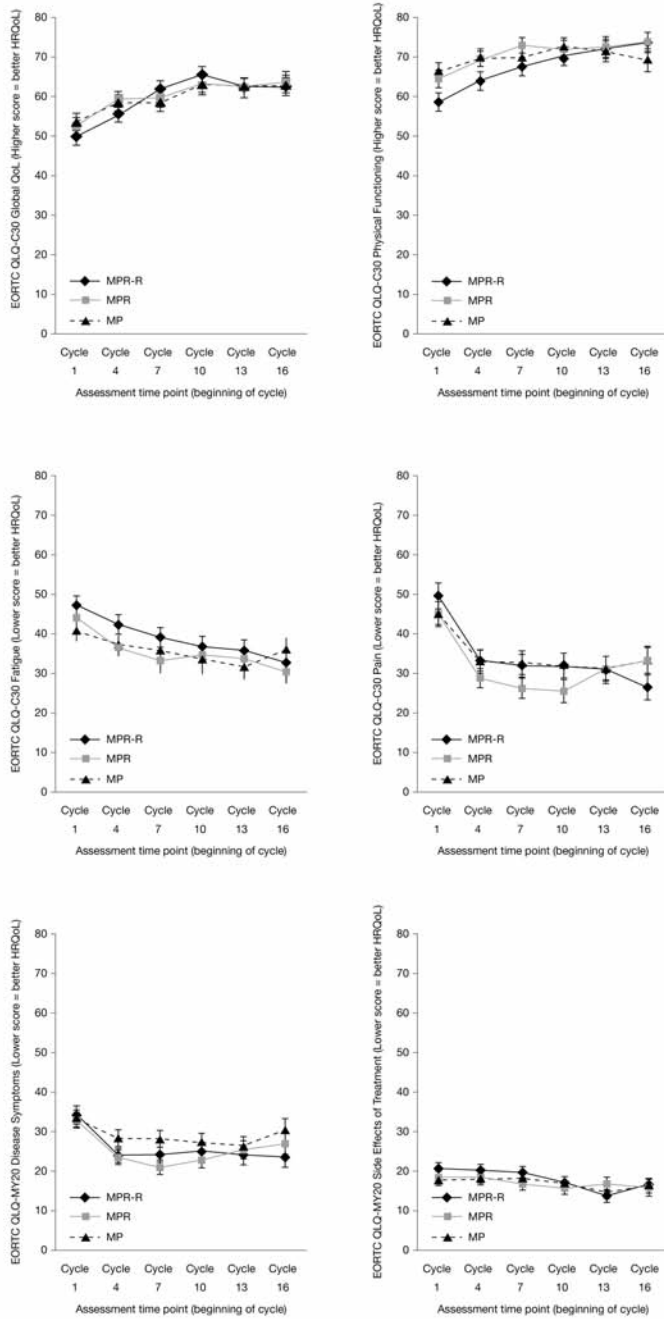
Figure S2. EORTC QLQ-C30 and QLQ-MY20 mean domain scores[a] with standard error bars by study arm during both induction and maintenance phases in patients aged 65-75 years.[b] [a]An increase in Global QoL and Physical Functioning scores represents an improvement in HRQoL, while the reverse applies to the other domain scores. Data during the induction phase were previously displayed as pooled score averages from the MPR-R and MPR arms,[6] 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.

	Global QoL	Physical Functioning	Fatigue	Pain	Disease Symptoms	Side Effects of Treatment
MPR-R	0.46*	0.43*	-0.23	-0.34	0.01	-0.2*
MPR	0.24	0.38*	-0.17	0.16	0.2	-0.16
MP	-0.07	-0.29#	0.17	0.31	0.3	-0.04

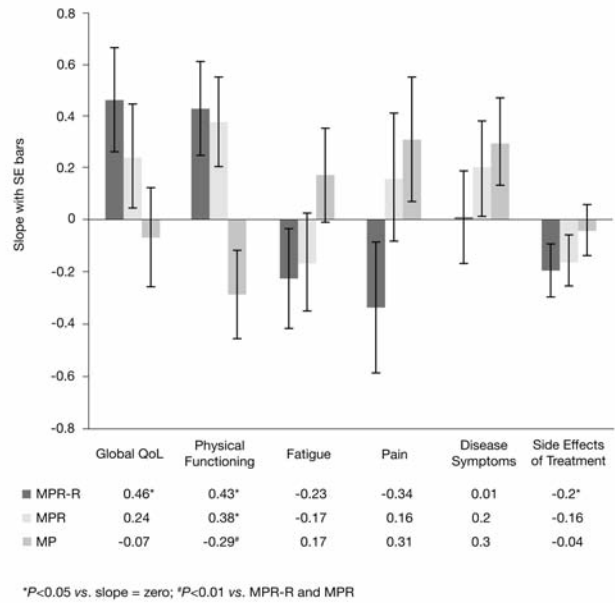*P<0.05 vs. slope = zero; #P<0.01 vs. MPR-R and MPR

Figure S3. Unadjusted mean changes (with standard error, SE, bars) per cycle from baseline (regression slopes from mixed models) in EORTC QLQ-C30 and QLQ-MY20 HRQoL domain scores during induction and maintenance phases in all patients.
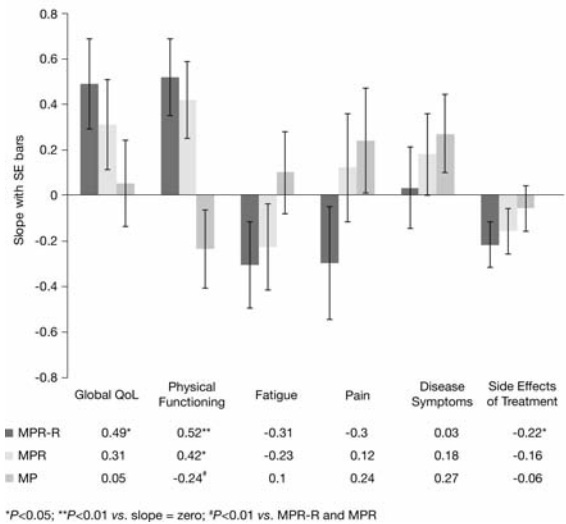

	Global QoL	Physical Functioning	Fatigue	Pain	Disease Symptoms	Side Effects of Treatment
MPR-R	0.49*	0.52**	-0.31	-0.3	0.03	-0.22*
MPR	0.31	0.42**	-0.23	0.12	0.18	-0.16
MP	0.05	-0.24#	0.1	0.24	0.27	-0.06

*P<0.05; **P<0.01 vs. slope = zero; #P<0.01 vs. MPR-R and MPR

Figure S4. Adjusted mean changes[a] (with standard error, SE, bars) per cycle from baseline (regression slopes from mixed models) in EORTC QLQ-C30 and QLQ-MY20 HRQoL domain scores during induction and maintenance phases in all patients. [a]Slopes are adjusted for baseline HRQoL score, age, sex, ISS stage, baseline beta-2 microglobulin, baseline renal function, and baseline plasma cell percentage.

(SD) renal function (glomerular filtration rate) was 64.7 (22.8), 62.9 (21.1), 63.0 (24.7) mL/min, respectively.

Compliance

Patient compliance with HRQoL reporting was high: compliance rates for each instrument during treatment until cycle 16
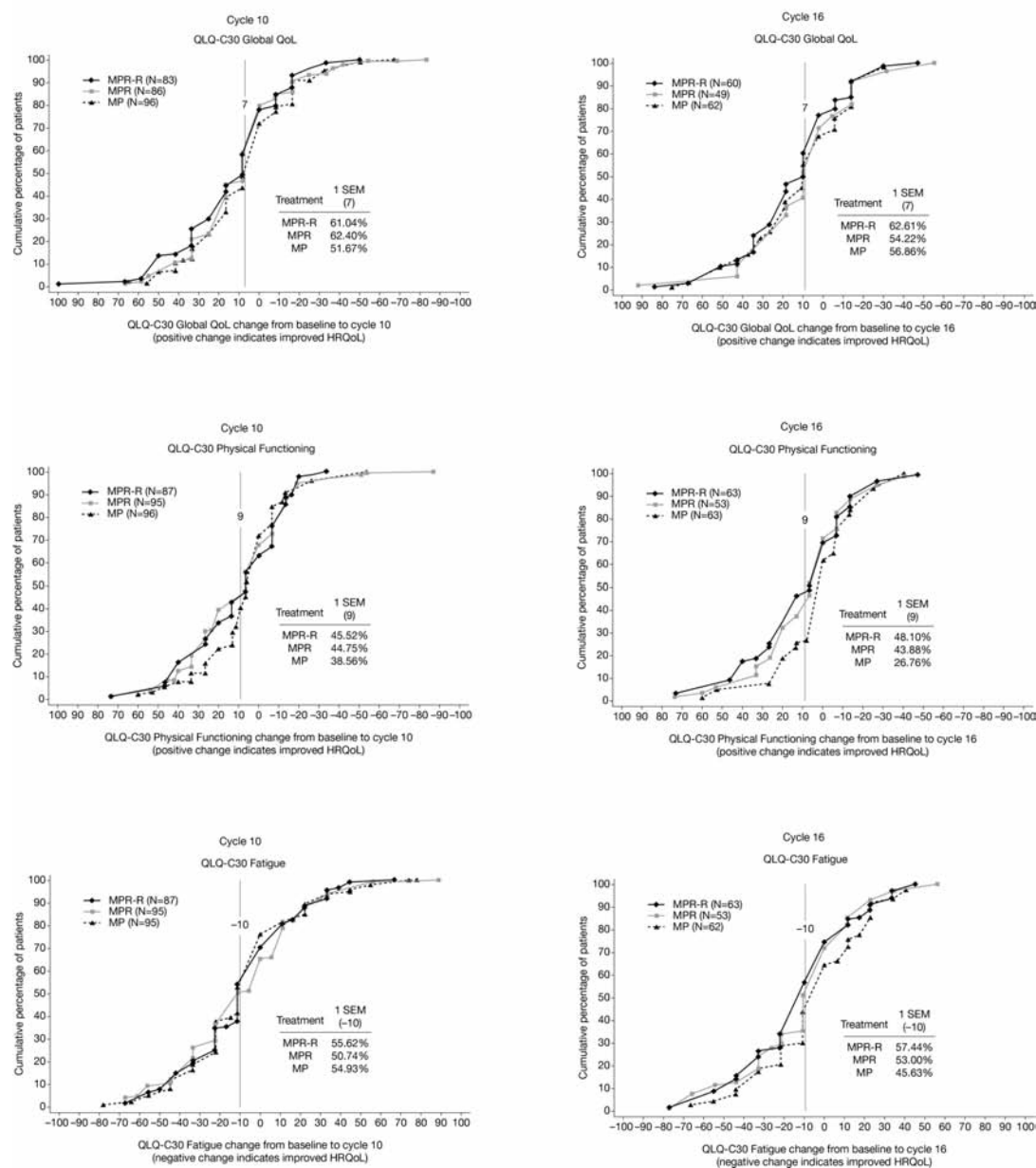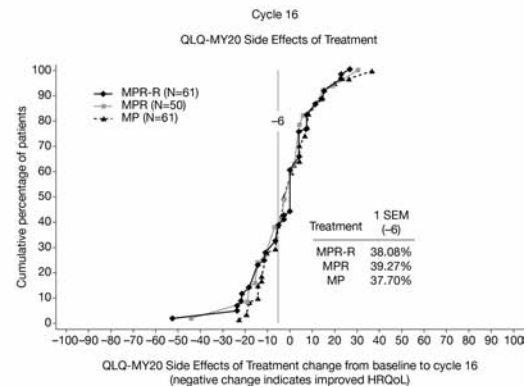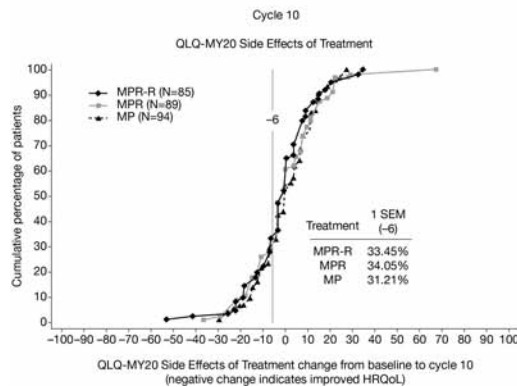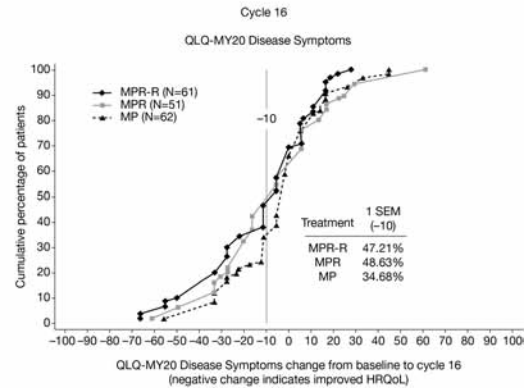
Figure S5. CDF curves during the maintenance phase at cycle 10 and cycle 16 for all patients.

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were consistently greater than 76% and generally ranged between 80% and 95% at each assessment, while compliance at PD/DC was at least 65%. There was no significant difference in compliance between treatment arms at any of the HRQoL measurement time points, with the only exception being MPR-R *versus* MP at cycle 7 for the QLQ-MY20 questionnaire (84% *vs.* 93%, respectively; *P*=0.036). Patients who had dropped out or who did not return their HRQoL questionnaires were significantly older at baseline than compliant patients at both cycles 10 and 16 (on average around 3 years; *P*<0.05). Patients who dropped out also had significantly poorer renal function and beta-2 microglobulin levels (*P*≤0.001) and had higher ISS stage

(*P*<0.05) at both cycles 10 and 16. Notably, however, these relationships were uniform across the treatment groups (no significant interaction terms). Consistent with this is the lack of significant differences in key demographic or clinical characteristics between the 3 treatment arms at cycles 10 or 16 suggesting that there was no significant difference between the treatment arms in the type of patients who dropped out or those who were non-compliant.

Health-related quality of life in patients aged 65–75 years

The improvement in HRQoL from baseline in MPR-R patients aged 65-75 years was slightly greater than that for all

Cycle 10
QLQ-C30 Pain

Cycle 16
QLQ-C30 Pain

Cycle 10
QLQ-MY20 Disease Symptoms

Cycle 16
QLQ-MY20 Disease Symptoms

Cycle 10
QLQ-MY20 Side Effects of Treatment

Cycle 16
QLQ-MY20 Side Effects of Treatment
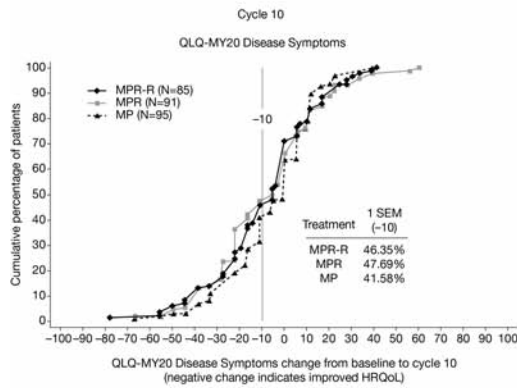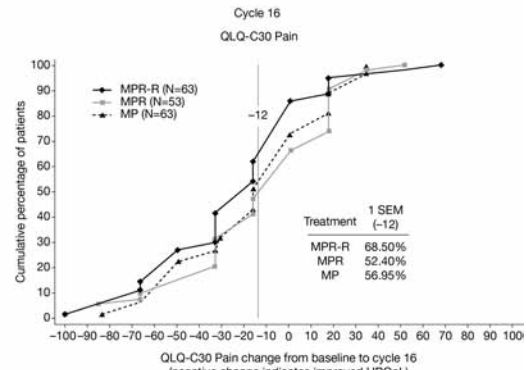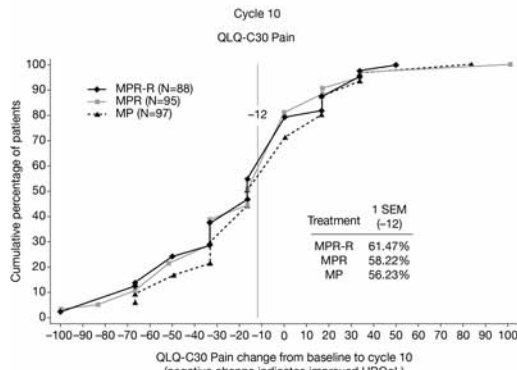
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MPR-R patients (*Online Supplementary Figure S2*). For example, mean Global QoL scores (SD) increased by 11.7 (24.2) from baseline to cycle 16 in MPR-R patients aged 65-75 years and by 11.3 (25.1) in all MPR-R patients. Similarly, mean Physical Functioning scores (SD) increased by 10.5 (24.4) and 10.2 (25.2) in these 2 groups, respectively; Fatigue scores decreased (i.e. improved) by 11.4 (26.0) and 10.1 (27.0); Pain scores improved by 23.3 (31.2) and 21.4 (33.0); Disease Symptoms scores improved by 12.4 (23.7) and 11.4 (23.2); and Side Effects of Treatment scores improved by 3.8 (13.6) and 2.6 (14.5). Comparable changes in HRQoL scores could not be replicated in the smaller subgroup of patients aged over 75 years.

Cumulative distribution frequency (CDF) graphs

CDF graphs of the change in HRQoL scores from baseline to cycles 10 and 16 for all patients and for patients aged 65-75 years (*Online Supplementary Figures S5 and S6*) demonstrated a differentiation in terms of clinically meaningful HRQoL improvements by comparing MPR-R with MPR and MP treatment during the maintenance phase of the trial. For each of the 6 HRQoL domains at both cycles 10 and 16, a higher percentage of patients receiving MPR-R achieved the MID compared with patients receiving MP alone; but only minimally higher for Side Effects of Treatment (*Online Supplementary Figure S7*). This was also true for patients aged 65-75 years (*Online Supplementary Figure S7*). Unlike with MP, however, which
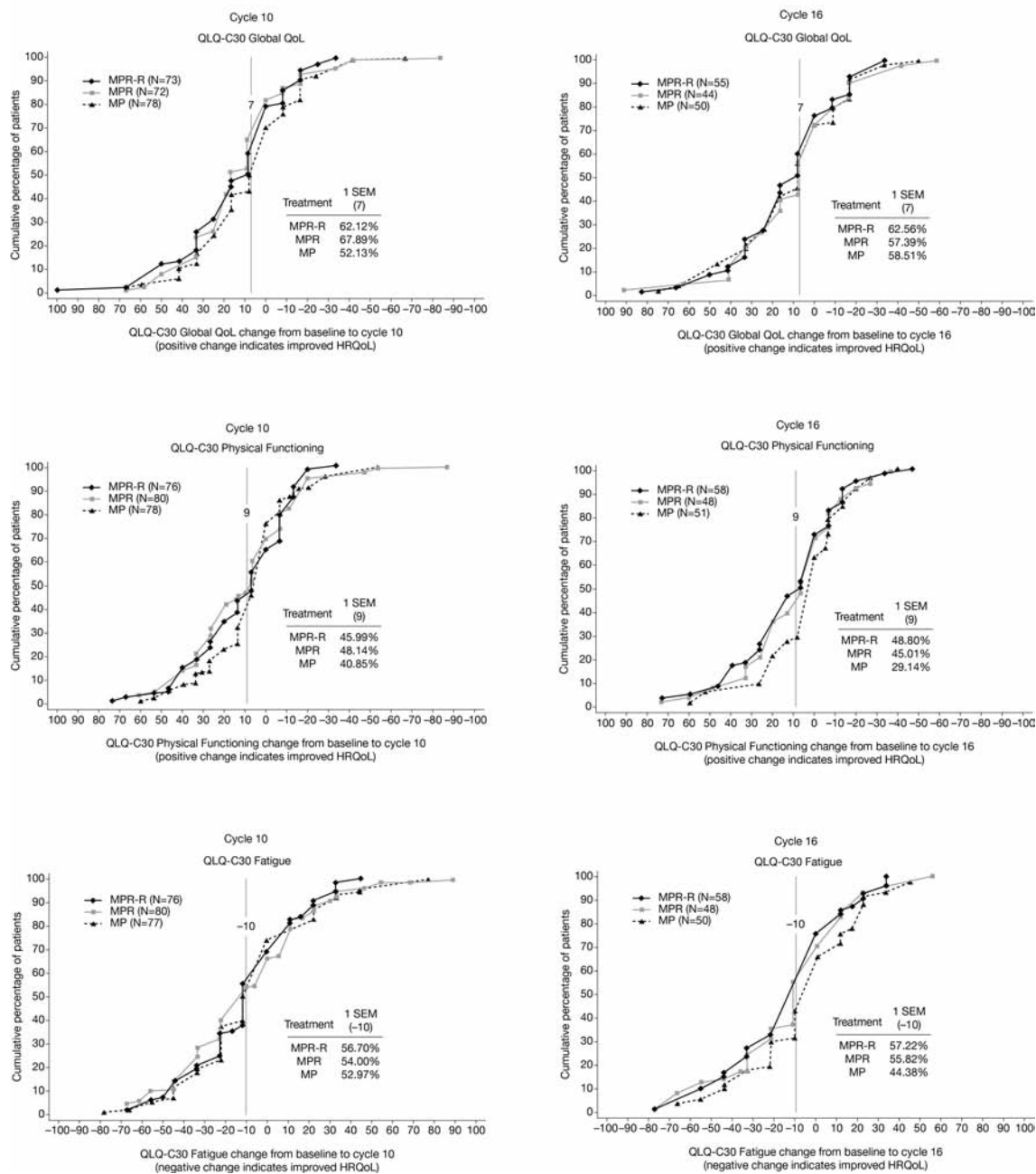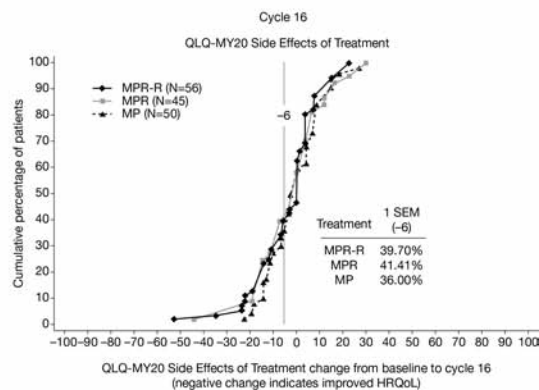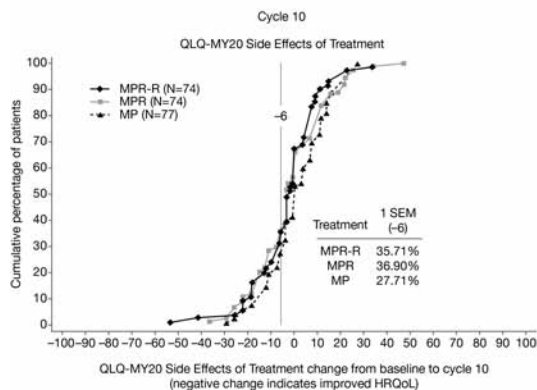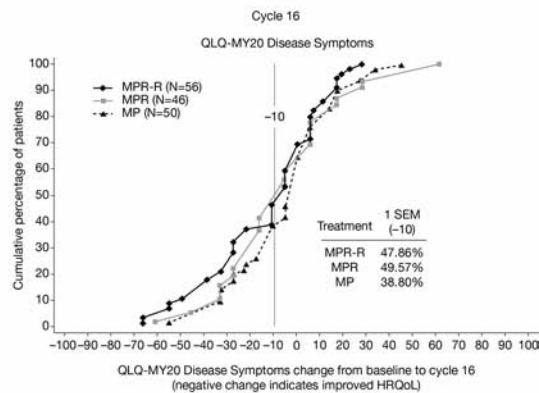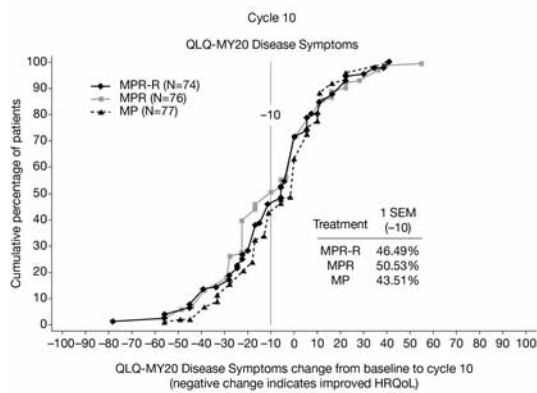
Figure S6. CDF curves during the maintenance phase at cycle 10 and cycle 16 for patients aged 65-75 years.

increased in only 3 domains, the percentage of MPR-R patients achieving MID increased between cycles 10 and 16 across all 6 HRQoL domains (though only minimally for Fatigue), a finding observed both for all patients and for the patient group aged 65-75 years (*Online Supplementary Figure S7*). Furthermore, the absolute percentage gap between MPR-R and MP patients achieving MID at cycle 16 *versus* 10, widened for Physical Functioning, Pain, Fatigue, and Disease Symptom scores, with a similar differentiation in these domains observed with the

CDF graphs as a whole (*Online Supplementary Figures S5* and *S6*). These differences between treatment arms in the proportion of patients reaching the MID, illustrated by the vertical line intersection with individual CDF curves in *Online Supplementary Figures S5* and *S6* were statistically significant at cycle 16 ($P<0.05$) for the comparison of Physical Functioning scores between patients receiving MPR-R and MP, although statistically non-significant for all other HRQoL domains considered at cycle 16 and all domains at cycle 10.

Cycle 10

QLQ-C30 Pain

MPR-R (N=77)
MPR (N=80)
MP (N=79)

−12

Treatment	1 SEM (−12)
MPR-R	63.98%
MPR	62.06%
MP	55.54%

Cumulative percentage of patients

QLQ-C30 Pain change from baseline to cycle 10
(negative change indicates improved HRQoL)

Cycle 16

QLQ-C30 Pain

MPR-R (N=58)
MPR (N=48)
MP (N=51)

−12

Treatment	1 SEM (−12)
MPR-R	70.48%
MPR	51.61%
MP	58.37%

Cumulative percentage of patients

QLQ-C30 Pain change from baseline to cycle 16
(negative change indicates improved HRQoL)

Cycle 10

QLQ-MY20 Disease Symptoms

MPR-R (N=74)
MPR (N=76)
MP (N=77)

−10

Treatment	1 SEM (−10)
MPR-R	46.49%
MPR	50.53%
MP	43.51%

Cumulative percentage of patients

QLQ-MY20 Disease Symptoms change from baseline to cycle 10
(negative change indicates improved HRQoL)

Cycle 16

QLQ-MY20 Disease Symptoms

MPR-R (N=56)
MPR (N=46)
MP (N=50)

−10

Treatment	1 SEM (−10)
MPR-R	47.86%
MPR	49.57%
MP	38.80%

Cumulative percentage of patients

QLQ-MY20 Disease Symptoms change from baseline to cycle 16
(negative change indicates improved HRQoL)

Cycle 10

QLQ-MY20 Side Effects of Treatment

MPR-R (N=74)
MPR (N=74)
MP (N=77)

−6

Treatment	1 SEM (−6)
MPR-R	35.71%
MPR	36.90%
MP	27.71%

Cumulative percentage of patients

QLQ-MY20 Side Effects of Treatment change from baseline to cycle 10
(negative change indicates improved HRQoL)

Cycle 16

QLQ-MY20 Side Effects of Treatment

MPR-R (N=56)
MPR (N=45)
MP (N=50)

−6

Treatment	1 SEM (−6)
MPR-R	39.70%
MPR	41.41%
MP	36.00%

Cumulative percentage of patients

QLQ-MY20 Side Effects of Treatment change from baseline to cycle 16
(negative change indicates improved HRQoL)

Discussion

The MID estimates in the MM-015 study range from 6 to 12 points, which is consistent with previously reported MIDs for QLQ-C30.[1] Although an MID for QLQ-C30 in MM patients of 6-17 points has been reported previously,[2] these estimates most notably applied an SD measure rather than the more common-ly accepted SEM-distribution-based approach, and thus did not take the reliability of the respective HRQoL domain into account. In other cancers, MIDs for QLQ-C30 have ranged from 5 to 10 points (breast cancer or small-cell lung cancer),[3] 5-14 (high-grade glioma)[4] and 2.5 to 8.5 (Global QoL QLQ C30 scores in localized prostate cancer).[5] No MIDs for QLQ-MY20 have been reported previously.

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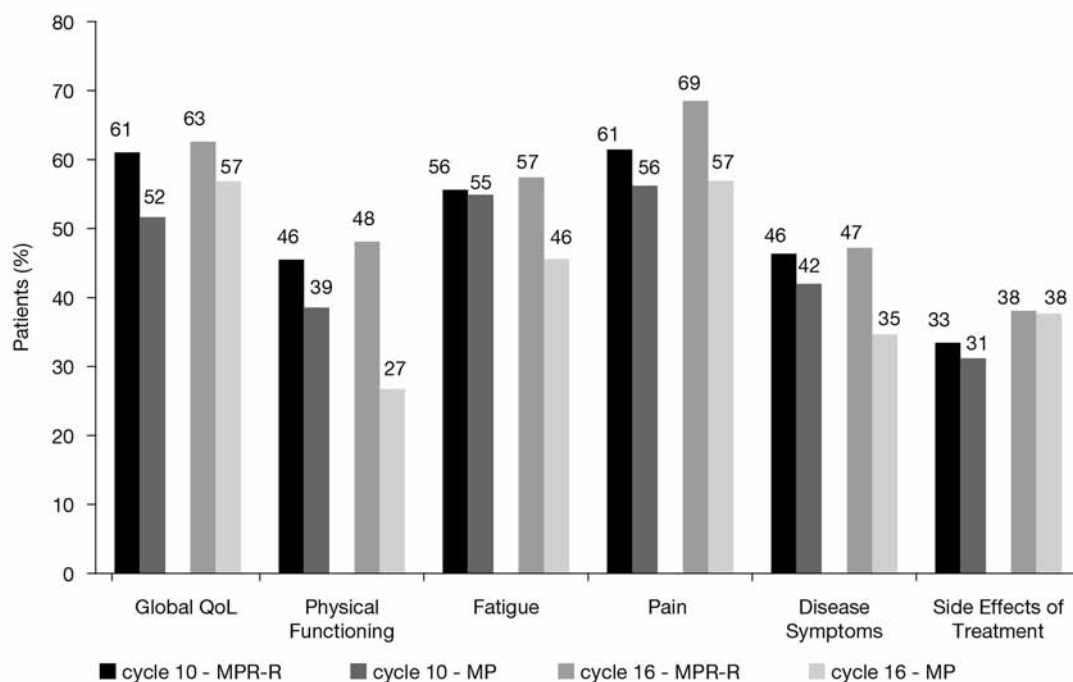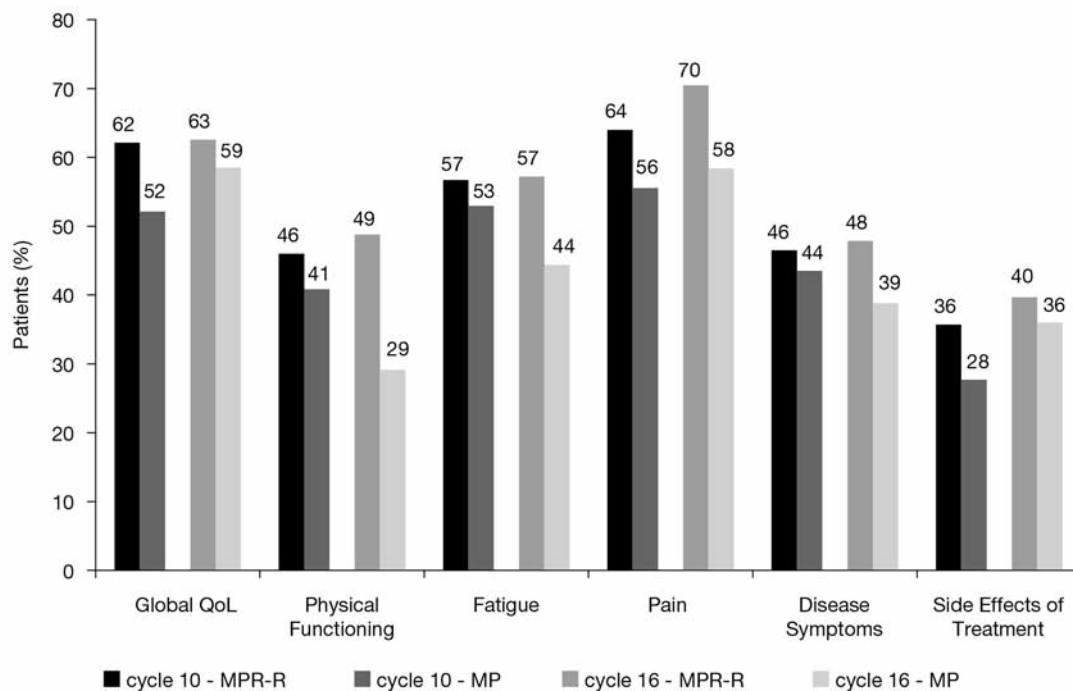
Figure S7. Percentage of (A) all patients and (B) patients aged 65–75 years receiving MPR-R or MP who reached the MID during the maintenance phase at cycles 10 and 16.

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