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Health-Related Quality of Life in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma: Findings From the Phase III MAIA Trial

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PURPOSE To evaluate the effects of daratumumab, lenalidomide, and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) on patient-reported outcomes (PROs) in the phase III MAIA study.

PATIENTS AND METHODS PROs were assessed on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item and the EuroQol 5-dimensional descriptive system at baseline and every 3 months during treatment. By mixed-effects model, changes from baseline are presented as least squares means with 95% CIs.

RESULTS A total of 737 transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma were randomly assigned to D-Rd (n = 368) or Rd (n = 369). Compliance with PRO assessments was high at baseline (> 90%) through month 12 (> 78%) for both groups. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item global health status scores improved from baseline in both groups and were consistently greater with D-Rd at all time points. A global health status benefit was achieved with D-Rd, regardless of age (< 75 and ≥ 75 years), baseline Eastern Cooperative Oncology Group (ECOG) performance status score, or depth of response. D-Rd treatment resulted in significantly greater reduction in pain scores as early as cycle 3 (P = .0007 v Rd); the magnitude of change was sustained through cycle 12. Reductions in pain with D-Rd were clinically meaningful in patients regardless of age, ECOG status, or depth of response. Similarly, PRO improvements were observed with D-Rd and Rd on the EuroQol 5-dimensional descriptive system visual analog scale score.

CONCLUSION D-Rd compared with Rd was associated with faster and sustained clinically meaningful improvements in PROs, including pain, in transplant-ineligible patients with newly diagnosed multiple myeloma regardless of age, baseline ECOG status, or depth of treatment response.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The introduction of novel agents to treat multiple myeloma (MM) has led to increased survival rates and delayed disease progression.¹⁻³ Use of induction, high-dose chemotherapy, and autologous stem-cell transplantation is the standard of care (SOC) for patients with newly diagnosed MM (NDMM) who are transplant eligible, typically those < 65 years of age.² Novel agents have also changed the management of transplant-ineligible (TIE) patients; combinations of lenalidomide and dexamethasone (Rd) or bortezomib, melphalan, and prednisone (VMP) have improved

survival outcomes and are the current SOC in these patients.⁴⁻⁶

Daratumumab is a human IgGκ anti-CD38 monoclonal antibody with a direct antitumor⁷⁻⁹ and immunomodulatory mechanism of action.¹⁰⁻¹³ In the phase III ALCYONE and MAIA studies, daratumumab in combination with VMP (D-VMP) or Rd (D-Rd) reduced the risk of disease progression or death by ≥ 44% and more than tripled the rate of minimal residual disease (MRD) negativity.^{14,15} The impact of therapy on patients' health-related quality of life (HRQoL) is an important outcome given the chronic nature of MM

CONTEXT

Key Objective

To evaluate the health-related quality of life of patients with transplant-ineligible, newly diagnosed multiple myeloma who received daratumumab, lenalidomide, and dexamethasone (D-Rd) or lenalidomide and dexamethasone alone in the phase III MAIA trial.

Knowledge Generated

Improvements in patient-reported outcomes were observed in both treatment groups; these improvements, including global health status and pain, were greater and more rapid in patients who received D-Rd compared with those who received lenalidomide and dexamethasone alone. Results were consistent across subgroups based on age, baseline Eastern Cooperative Oncology Group performance status, and depth of treatment response.

Relevance

The patient-reported outcomes from the MAIA trial provide additional evidence of the benefits of D-Rd in patients with transplant-ineligible, newly diagnosed multiple myeloma.

and is especially relevant for older patients or those with comorbidities who are TIE.¹⁶

Here, we present the impact of treatment on patient-reported outcomes (PROs) in the MAIA study.

PATIENTS AND METHODS

Study Design and Patients

Details of the MAIA study have been published previously.¹⁵ Briefly, MAIA was a randomized, open-label, active-controlled, multicenter, phase III study of TIE patients with NDMM. Eligible patients were ≥ 18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 . Patients were randomly assigned 1:1 to receive D-Rd or Rd. Patients in both treatment groups received lenalidomide 25 mg orally once a day on days 1 through 21 of each 28-day cycle until disease progression or unacceptable toxicity, and dexamethasone 40 mg orally or by IV once a week until disease progression or unacceptable toxicity. Patients received daratumumab intravenously 16 mg/kg once weekly for the first 8 weeks (cycles 1 and 2) of treatment, every other week for 16 weeks (cycles 3-6), and every 4 weeks thereafter (cycle 7 and beyond). Treatment was continued until disease progression or unacceptable toxicity.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Institutional review boards of all participating institutions approved the study Protocol. All patients provided written informed consent.

PRO Instruments

PROs were collected using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30)^{17,18} and the EuroQol 5-dimensional descriptive system (EQ-5D-5L)¹⁹ instruments.

The EORTC QLQ-C30 includes 30 items comprising five functional scales (physical, role, emotional, cognitive, and

social functioning), one global health status (GHS) scale, three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week. Higher scores represent better GHS and functioning and greater (ie, worse) symptoms. GHS score change from baseline was a secondary end point; other scales were included as exploratory end points.

EQ-5D-5L evaluates five dimensions of health status (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and includes a visual analog scale (VAS)²⁰ with scores rated from 0 (worst imaginable health) to 100 (best imaginable health). The EQ-5D-5L also includes a utility value (also referred to as an index value). This value is derived from the scores on each of the five dimensions but is not technically a PRO and is not reported here.

Patients completed the questionnaires using an electronic device prior to the administration of study intervention or study assessments at baseline (≤ 21 days from random assignment) on day 1 of cycles 3, 6, 9, and 12, and every sixth cycle thereafter until the end of treatment.

Statistical Analyses

The PRO analyses included patients in the intent-to-treat (ITT) population from the interim analysis (median follow-up: 28.0 months).¹⁵ Data through cycle 12 are reported for patients while on treatment (D-Rd or Rd), and data past this time point are not included because of PRO compliance rates and limited follow-up. Change from baseline in QLQ-C30 GHS scores, functional scale and symptom scale scores, and EQ-5D-5L VAS scores was assessed in the ITT population and in post hoc subgroups stratified by age (< 75 and ≥ 75 years), ECOG PS (0, 1-2), and depth of treatment response (best response of complete response [CR] or better, very good partial response [VGPR], and partial response [PR] or better).

Compliance rate was calculated at baseline and for each post-treatment PRO assessment visit as a percentage, with the number of assessments received divided by the number of assessments expected at that time point (a clinical prediction of how many patients will be on treatment).

Change from baseline in PRO scores at each time point was analyzed using a mixed-effects model for repeated measurements including baseline value, visit, treatment, visit-by-treatment interaction, and random assignment stratification factors (ie, International Staging System [I v II v III], region [North America v other], and age [< 75 years v ≥ 75 years]) as fixed effects and individual subject as random effect. Results for overall population and subgroups are presented as least squares (LS) means with 95% CIs; *P* values were based on the treatment difference of the LS mean change from baseline (D-Rd–Rd).

For each PRO, the minimally important difference threshold for clinically meaningful change from baseline was defined a priori based on published literature: a change of ≥ 8 points for the EORTC QLQ-C30 GHS score²¹; a change of ≥ 10 in the EORTC QLQ-C30 functional and symptom scores²¹; and a change of ≥ 7 points for the EQ-5D-5L VAS score.²² The median time to improvement or worsening was calculated using the Kaplan-Meier method. The Cochran-Mantel-Haenszel estimate of the common odds ratio (OR) adjusted for stratification variables was used. An OR of > 1 indicates an advantage for D-Rd treatment. Hazard ratios (HRs) were estimated based on the Cox proportional hazard model adjusted with stratification factors. No adjustments were made for multiplicity as this was an exploratory analysis; nominal *P* values are presented.

RESULTS

Baseline Characteristics and PRO Compliance Rates

A total of 737 patients were randomly assigned to D-Rd ($n = 368$) or Rd ($n = 369$) (Appendix Fig A1, online only). The median age was 73 years (range, 45-90 years). Baseline characteristics were balanced between groups.¹⁵ Mean baseline values for PROs were similar between the treatment groups and reflected the impairment of patients' HRQoL at study entry (Table 1). The proportion of patients reporting various levels of pain at baseline was consistent between D-Rd and Rd: no pain at all (25% v 23%); a little bit of pain (27% v 28%); quite a bit of pain (21% v 28%); and very much pain (27% v 20%).

Compliance with PRO assessments was high and similar in both treatment groups across all time points, with rates of $> 90\%$ at baseline and $> 78\%$ through cycle 12 (Appendix Table A1, online only).

Treatment Effect on EORTC QLQ-C30 GHS Scores

ITT population. EORTC QLQ-C30 GHS scores improved in both treatment groups across all time points (Fig 1A), with

TABLE 1. Baseline Demographics and Disease Characteristics (ITT Population)

Characteristic	D-Rd (n = 368)	Rd (n = 369)
Age, y		
< 75, n (%)	208 (56.5)	208 (56.4)
≥ 75 , n (%)	160 (43.5)	161 (43.6)
Female, n (%)	179 (48.6)	174 (47.2)
Baseline ECOG score ^a , n (%)		
0	127 (34.5)	123 (33.3)
1	178 (48.4)	187 (50.7)
2	63 (17.1)	59 (16.0)
EORTC QLQ-C30 scores ^b	n = 354	n = 348
Global health status	56.7 (24.8)	56.2 (24.2)
Physical functioning	63.9 (28.7)	66.5 (26.2)
Role functioning	58.2 (37.1)	59.5 (34.4)
Emotional functioning	72.3 (24.0)	69.0 (24.4)
Cognitive functioning	79.4 (24.6)	80.5 (23.1)
Social functioning	69.9 (34.4)	71.5 (30.4)
Pain	47.4 (36.7)	44.8 (33.8)
Fatigue	43.5 (29.0)	42.9 (27.5)
Nausea or vomiting	7.5 (17.8)	8.2 (17.8)
Dyspnea	26.2 (29.6)	25.6 (30.7)
Insomnia	31.0 (31.5)	34.5 (33.4)
Appetite loss	27.1 (33.6)	26.9 (31.8)
Constipation	27.2 (33.3)	25.4 (32.9)
Diarrhea	8.4 (18.2)	8.0 (19.9)
Financial difficulties	9.0 (19.2)	8.8 (19.9)
EQ-5D-5L scores	n = 349	n = 346
VAS ^c	62.6 (22.3)	62.7 (21.6)

NOTE. Data are expressed as mean (SD), unless stated otherwise.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L, EuroQol 5-dimensional descriptive system; GHS, global health status; ITT, intent to treat; VAS, visual analog scale.

^aOn a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.

^bScores range from 0 to 100, with a higher score indicating better health.

^cScores range from 0 to 100, with a high score indicating a high level of self-evaluated health status.

significantly greater improvement from baseline to cycle 3 in the D-Rd versus Rd group (4.5 [95% CI, 2.4 to 6.6] v 1.5 [95% CI, -0.7 to 3.7]; *P* = .0454). Median time to GHS improvement was 1 month shorter with D-Rd (2.1 months; range, 1.8-27.4) than Rd (3.1 months; range, 1.7-27.0), and the median time to worsening was 1 month longer with D-Rd (22.5 months; range, 17.4-32.2) than Rd (21.1 months; range, 10.9-24.3), although these differences were not statistically significant. Mean changes from baseline improved over time for the functioning

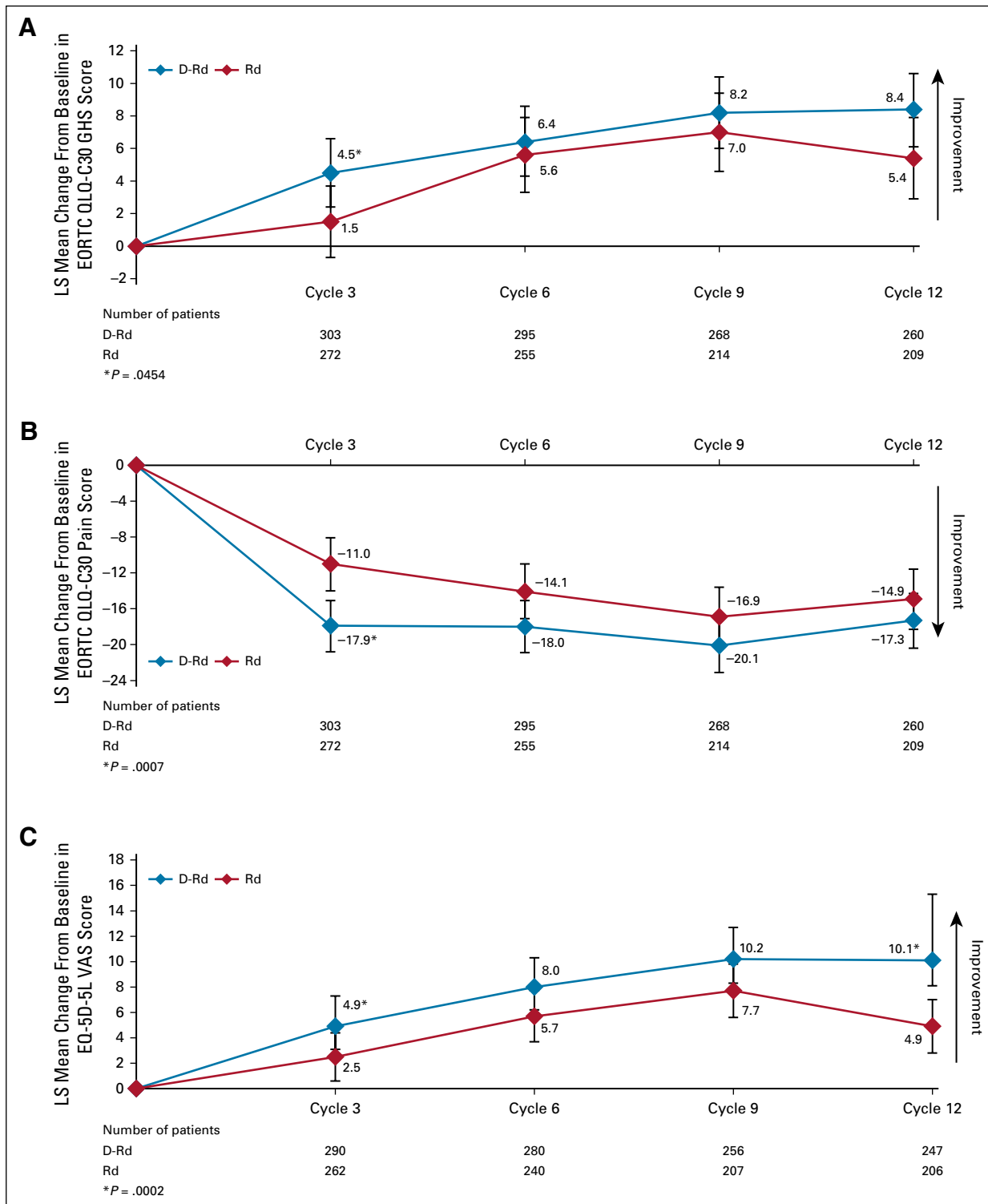


FIG 1. Change from baseline in (A) EORTC QLQ-C30 GHS score, (B) EORTC QLQ-C30 pain score, and (C) EQ-5D-5L VAS score (intent-to-treat population). EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L, EuroQol 5-dimensional descriptive system; GHS, global health status; VAS, visual analog scale.

scales and for the fatigue and nausea or vomiting symptom scales, with no statistically significant differences between treatment groups (Appendix Table A2, online only).

A significantly greater reduction from baseline in pain scores was reported early (cycle 3) in the D-Rd (−17.9 [95% CI, −20.7 to −15.0]) versus Rd group (−11.0 [95%

CI, -14.0 to -8.1]; $P = .0007$); the magnitude of change was generally sustained through cycle 12 (Fig 1B). These results were confirmed by a sensitivity analysis using a pattern-mixture model.

The proportion of patients in each treatment group who experienced PRO improvement or worsening at any point during treatment is shown in Table 2. Greater proportions of patients reported meaningful improvement with D-Rd compared with Rd in fatigue (62.2% v 52%) and physical functioning (49.7% v 40.9%). For all PROs, patients in the D-Rd group were significantly more likely to experience improvement than those in the Rd group.

Subgroups by age, baseline ECOG, and depth of response.

GHS score improvements from baseline were observed with D-Rd as early as cycle 3 regardless of age and were greater in magnitude with D-Rd than Rd at most time points (Figs 2A and 2B). Early after treatment with D-Rd (cycle 3), patients age < 75 years showed a greater magnitude of improvement in the GHS score (6.8 [95% CI, 4.1 to 9.5]) than in those age \geq 75 years (1.7 [95% CI, -1.3 to 4.7]). In both treatment groups, GHS was maintained in patients with ECOG PS 0 (Fig 2C) and improved from baseline in those with an ECOG PS of 1-2 (Fig 2D). GHS score improvements with D-Rd were greater than Rd at all time points in the ECOG PS 1-2 subgroup and were sustained through cycle 12. In patients who achieved a PR or better, GHS scores improved from baseline in both treatment

groups but were numerically greater with D-Rd than Rd at all time points (Appendix Table A2). Similarly, GHS scores improved from baseline in the D-Rd group among patients with a CR or better and VGPR.

Patients also reported early and greater reductions in pain with D-Rd versus Rd regardless of age (Figs 3A and 3B). Patients with an ECOG PS of 0 reported reductions from baseline in pain scores with D-Rd and Rd; the reductions were greater with D-Rd and sustained through cycle 12 (Fig 3C). The trend for improvement was similar but greater in magnitude in patients with an ECOG PS of 1-2, with reductions from baseline in pain scores at all time points in both treatment groups (Fig 3D). Time to worsening of GHS, symptoms, and functioning was generally longer with greater depth of clinical response (Table 3). Patients who achieved a PR or better had reductions in pain in both treatment groups across all time points, with greater reductions with D-Rd versus Rd at cycles 3 and 6 (Appendix Table A2). Patients with VGPR or a CR or better also reported reduced pain with D-Rd versus Rd as early as cycle 3.

Treatment Effect on EQ-5D-5L VAS Scores

ITT population. EQ-5D-5L VAS scores improved from baseline in both treatment groups (Fig 1C), with significantly greater improvement with D-Rd versus Rd at cycle 12 (10.1 [95% CI, 8.1 to 12.1] v 4.9 [95% CI, 2.8 to 7.0]; $P = .0002$).

TABLE 2. Proportion of Patients Who Experienced Improvement or Worsening of PROs at Any Time on Treatment With ORs

PRO	Improvement			Worsening		
	Rd	D-Rd	OR ^a (95% CI)	Rd	D-Rd	OR ^a (95% CI)
EQ-5D-5L						
VAS	50.4	54.3	1.17 (0.88 to 1.56)	42.8	44.8	1.09 (0.81 to 1.45)
Global health status/QoL						
Global health status	48.5	52.7	1.18 (0.89 to 1.58)	40.9	43.8	1.12 (0.84 to 1.50)
Functional scales						
Physical functioning	40.9	49.7	1.43 (1.07 to 1.91)	39.6	38.6	0.96 (0.71 to 1.29)
Role functioning	45.5	52.7	1.33 (1.00 to 1.78)	49.1	52.2	1.13 (0.85 to 1.51)
Emotional functioning	42.5	47.0	1.20 (0.90 to 1.60)	35.5	36.1	1.03 (0.76 to 1.39)
Cognitive functioning	34.4	36.1	1.08 (0.80 to 1.46)	49.6	57.3	1.37 (1.02 to 1.83)
Social functioning	38.5	45.4	1.33 (0.99 to 1.78)	50.7	51.1	1.02 (0.76 to 1.36)
Symptom scales						
Fatigue	52.0	62.2	1.52 (1.13 to 2.04)	57.2	60.3	1.14 (0.85 to 1.53)
Nausea and vomiting	18.2	18.8	1.04 (0.72 to 1.51)	34.4	38.6	1.20 (0.89 to 1.62)
Pain	59.6	65.2	1.27 (0.94 to 1.71)	40.7	37.8	0.89 (0.66 to 1.19)

Abbreviations: D-Rd, daratumumab, lenalidomide, and dexamethasone; EQ-5D-5L, EuroQol 5-dimensional descriptive system; OR, odds ratio; QoL, quality of life; PRO, patient-reported outcome; Rd, lenalidomide and dexamethasone; VAS, visual analog scale.

^aImprovement or worsening defined as increase or decrease in score equal to at least half of standard deviation from baseline values, where standard deviation is calculated from the scores at baseline combining both treatment groups. OR based on the Cochran-Mantel-Haenszel estimate. ORs for improvement > 1 and ORs for worsening < 1 favor D-Rd.

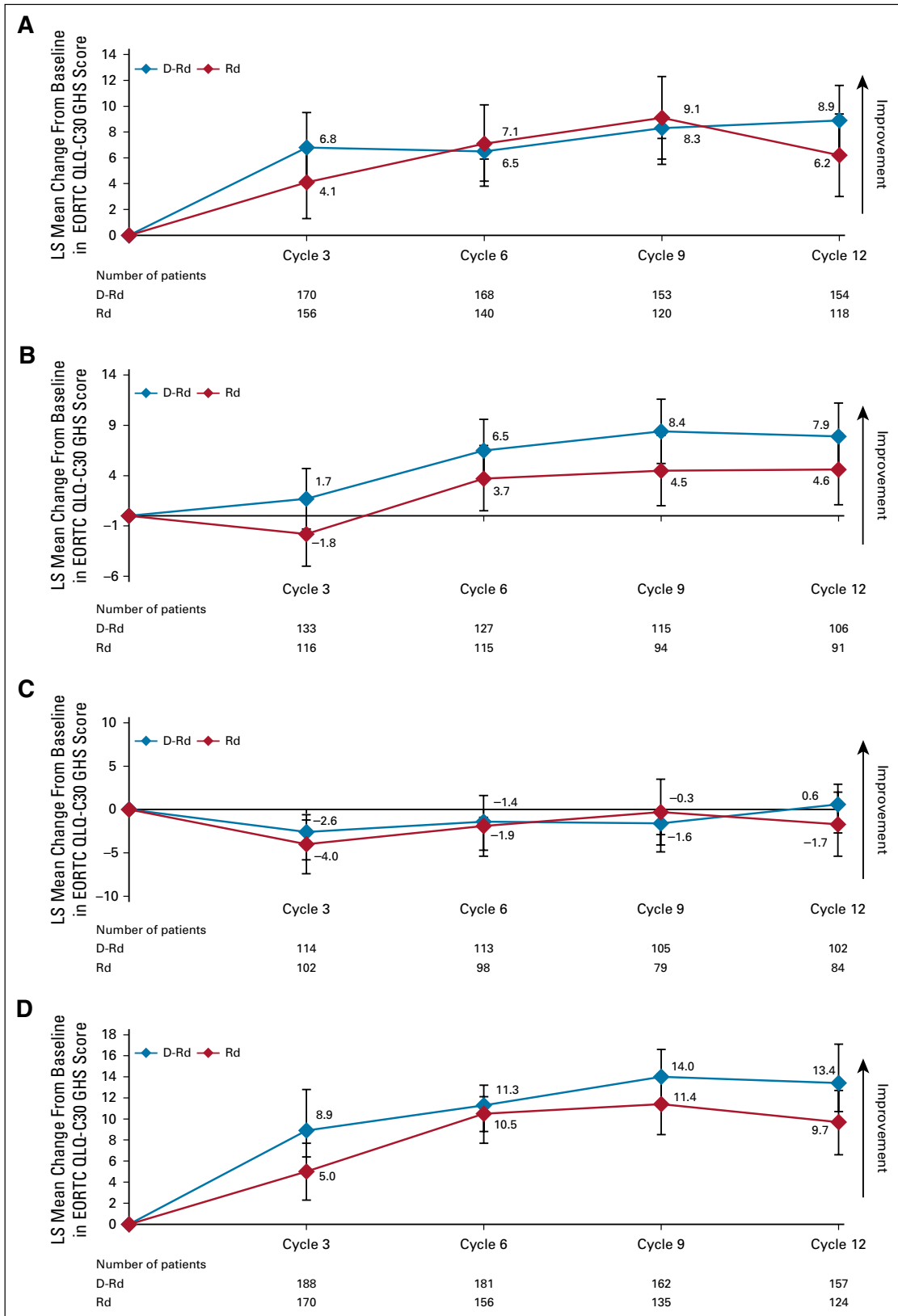


FIG 2. Change from baseline in the EORTC QLQ-C30 GHS score in subgroups of patients (A) < 75 years of age, (B) ≥ 75 years of age, (C) ECOG of 0, and (D) ECOG of 1-2. ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; GHS, global health status.

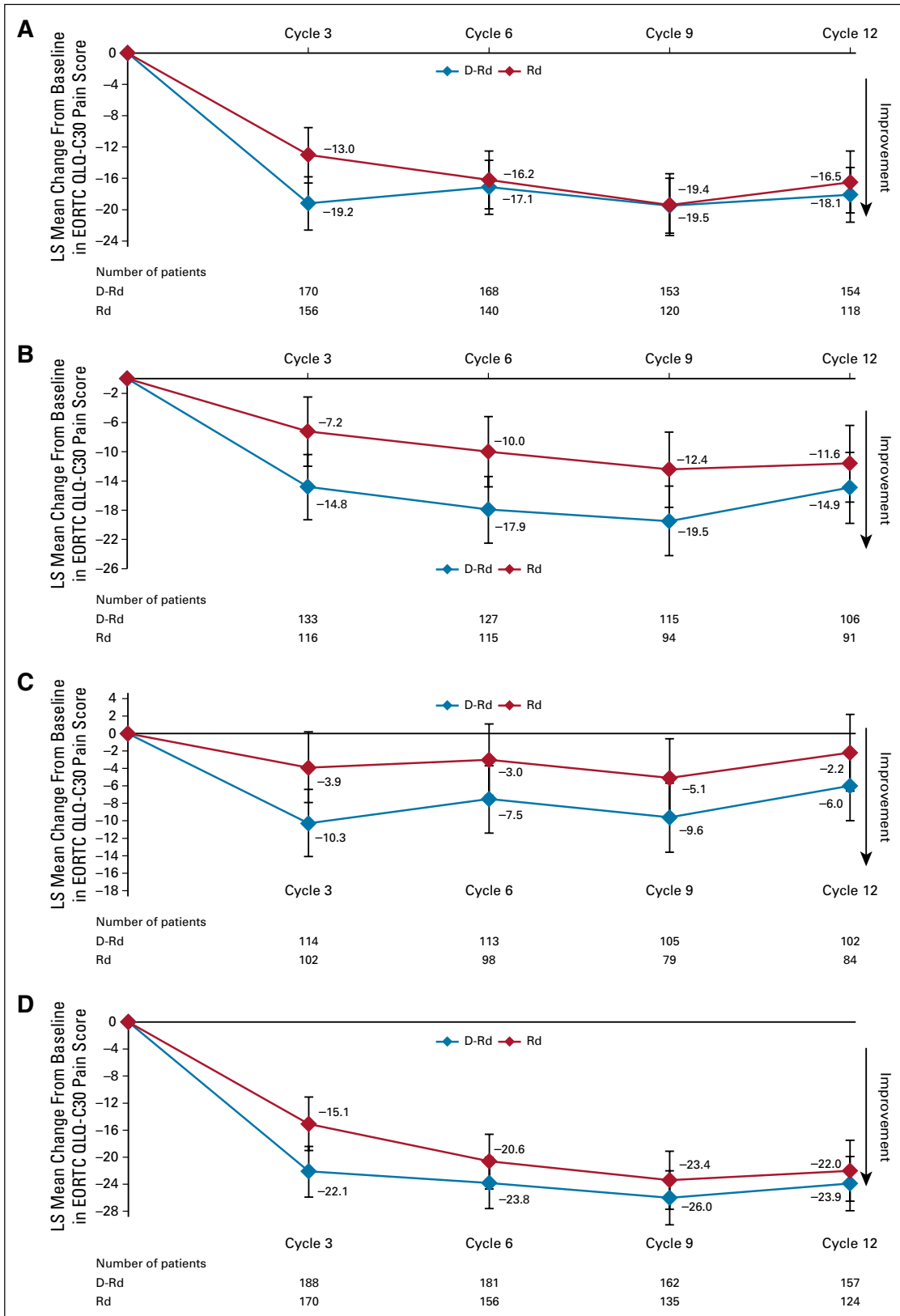


FIG 3. Change from baseline in the EORTC QLQ-C30 pain score in subgroups of patients (A) < 75 years of age, (B) ≥ 75 years of age, (C) ECOG of 0, and (D) ECOG of 1-2. ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item.

TABLE 3. HRs for Comparison of Time to Worsening of EORTC QLQ-C30 Scores by Depth of Response and MRD Status for Pooled Treatment Arms

EORTC QLQ-C30 Scale	Clinical Response					
	(s)CR v VGPR/PR		SD v VGPR/PR		MRD- v MRD+	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
GHS ^a	0.72 (0.60 to 0.86)	.0004	1.57 (1.17 to 2.12)	.0031	0.67 (0.54 to 0.84)	.0004
Physical functioning	0.87 (0.73 to 1.04) ^b	.135 ^b	1.51 (1.10 to 2.05) ^a	.0097 ^a	0.75 (0.60 to 0.93) ^a	.0088 ^a
Role functioning ^a	0.84 (0.71 to 0.99)	.0335	1.32 (1.00 to 1.75)	.0484	0.76 (0.63 to 0.92)	.0054
Emotional functioning ^a	0.79 (0.65 to 0.96)	.0159	1.49 (1.08 to 2.07)	.016	0.78 (0.62 to 0.98)	.0303
Cognitive functioning	0.87 (0.75 to 1.01) ^b	.0695 ^b	1.16 ^b (0.87 to 1.55)	.3141 ^b	0.93 (0.78 to 1.11) ^c	.44 ^c
Social functioning	0.85 (0.72 to 0.99) ^a	.045 ^a	1.23 (0.92 to 1.64) ^b	.1661 ^b	0.76 (0.63 to 0.93) ^a	.0069 ^a
Pain ^a	0.70 (0.59 to 0.84)	.0001	1.58 (1.17 to 2.13)	.0027	0.64 (0.51 to 0.79)	< .0001
Fatigue	0.93 (0.80 to 1.08) ^c	.3511 ^c	1.26 (0.97 to 1.64) ^b	.0896 ^b	0.90 (0.75 to 1.07) ^b	.2357 ^b
Nausea or vomiting	0.91 (0.76 to 1.09) ^c	.3016 ^c	1.13 (0.80 to 1.59) ^b	.4819 ^b	0.84 (0.68 to 1.04) ^b	.1066 ^b
Dyspnea ^a	0.64 (0.54 to 0.77)	< .0001	1.30 (0.96 to 1.76)	.094	0.67 (0.54 to 0.83)	.0002
Insomnia	0.88 (0.74 to 1.04) ^b	.1293 ^b	1.23 (0.91 to 1.67) ^b	.1721 ^b	0.93 (0.76 to 1.12) ^c	.4251 ^c
Appetite loss	0.88 (0.74 to 1.06) ^b	.1751 ^b	1.45 (1.06 to 1.97) ^a	.02 ^a	0.76 (0.61 to 0.94) ^a	.0207 ^a
Constipation	0.93 (0.78 to 1.11) ^c	.4087 ^c	1.37 (1.01 to 1.85) ^a	.04 ^a	0.97 (0.78 to 1.19) ^c	.7898 ^c
Diarrhea	0.97 (0.82 to 1.14) ^c	.6809 ^c	1.15 (0.83 to 1.59) ^b	.4114 ^b	0.97 (0.81 to 1.17) ^c	.784 ^c

NOTE. Worsening of EORTC QLQ-C30 defined as a ≥ 10 -point decrease, and worsening of EORTC QLQ-C30 pain and fatigue was defined as a ≥ 10 -point increase.

Abbreviations: CR, complete response; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; GHS, global health score; HR, hazard ratio; HRQoL, health-related quality of life; MRD, minimal residual disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

^aStatistical significance for better response associated with delay in worsening HRQoL.

^bTrend for better response associated with delay in worsening HRQoL.

^cNo clear evidence of relation response.

Subgroups by age, baseline ECOG, and depth of response.

Similar to the subgroup analyses of EORTC QLQ-C30 functional and symptom scale scores, patients in both groups experienced improvements from baseline in VAS scores regardless of age, ECOG PS, and depth of response; improvements were greater with D-Rd at all time points (Appendix Table A2).

DISCUSSION

PROs are important to understand patients' perspectives in chronic diseases such as MM and may be useful to engage patients and providers in treatment decision making.²³ TIE patients with NDMM from the MAIA trial showed early and substantial PRO improvements from baseline during treatment with D-Rd compared with Rd alone. Improvements in EORTC QLQ-C30 GHS, functional scales, and pain scores were sustained through the duration of the study. Similar trends were observed for improvements in EQ-5D-5L VAS scores. Results were consistent between a mixed-effects model for repeated measurements and a pattern-mixture model.

These PRO improvements reflect the rapid and deep responses with daratumumab reported previously in the MAIA trial.¹⁵ At the median follow-up of 28 months, the

progression-free survival (PFS) HR in the D-Rd versus Rd group was 0.56 (95% CI, 0.43 to 0.73; $P < .0001$). The overall response rate with D-Rd was improved versus Rd (93% v 81%; $P < .0001$), with a greater proportion of patients in the D-Rd group than the Rd group achieving a CR or better (47.6% v 24.9%, $P < .0001$) and a VGPR or better (79.3% v 53.1%, $P < .0001$). The MRD-negativity rate (at a threshold of 10^5) for D-Rd versus Rd was 24% versus 7% ($P < .0001$). PFS with D-Rd was also shown to be superior over Rd in subgroups by age and ECOG PS. The median relative dose intensity of lenalidomide was lower, and rates of dose discontinuations or modifications of lenalidomide therapy due to adverse events were higher among patients who were ≥ 75 versus < 75 years of age.²⁴

PRO improvements were noted with D-Rd compared with Rd regardless of age, ECOG PS, or depth of response. In the subgroup analysis of patients who were < 75 years and ≥ 75 years of age, D-Rd treatment resulted in substantial improvements from baseline in HRQoL as early as cycle 3. More patients stayed on D-Rd for a longer period of time with improved GHS. Additionally, GHS score improvements from baseline to cycle 3 were numerically greater in the < 75 -year group than the ≥ 75 -year group. The reason for this is unclear but may be attributed to the negative impact

of lenalidomide therapy on HRQoL in this subgroup, as reflected in the median relative dose intensity and rates of dose discontinuations or modifications. Nevertheless, D-Rd–treated patients age ≥ 75 years experienced sustained GHS improvements from baseline that were clinically meaningful in later cycles. This is an important finding given that older patients with cancer typically experience a decline in general health and functional capacities over time.^{25,26}

The symptom burden is high in patients with MM, and pain in particular has a strong negative impact on HRQoL.²⁷ Patients reported significant reductions in pain early after D-Rd treatment, which were sustained through cycle 12, including an increase (11.4 months delay) in the time to worsening of pain scores. These reductions were clinically meaningful regardless of age and despite nearly half of the patients reporting quite a bit of pain or very much pain at baseline. Early and sustained pain relief has been shown to yield greater treatment satisfaction in patients with cancer²⁸ yet remains an unmet need. These results may provide a meaningful metric for patients and physicians to inform therapeutic decisions in clinical practice.

ECOG PS has been shown to be independently associated with HRQoL in patients with MM, with higher ECOG PS (eg, ≥ 2) correlating with lower patient-perceived effectiveness of treatment.²⁹⁻³¹ In this analysis, HRQoL was improved or maintained with treatment regardless of ECOG PS, with greater improvements in GHS and pain in the D-Rd versus Rd group. These improvements, which were clinically meaningful and sustained through cycle 12, were achieved in a cohort of patients in which most (approximately 70%) had an ECOG PS of 1 or 2 at baseline.

Previous studies have shown an association between depth of clinical response and HRQoL outcomes in patients with MM.^{32,33} Our findings are consistent with those reports, with patients with deep responses (a CR or better) demonstrating early and sustained clinically meaningful improvements in GHS and pain with D-Rd and Rd; similar trends were observed in patients who achieved VGPR or a PR or better. Trends for HRQoL improvements in the EQ-5D-5L VAS score were similar.

Cross-trial comparisons are often difficult because of differences in patient populations, treatment regimens, and PRO measures. Nevertheless, HRQoL improvements in Rd-treated patients in our analysis are consistent with clinically meaningful HRQoL improvements seen with Rd in the FIRST trial with TIE patients with NDMM.³⁴ HRQoL improvements in the current analysis of an older population (median age, 73 years) are in line with the results of the ALCYONE study of D-VMP, involving a similar population of

TIE patients with NDMM.³⁵ This suggests a broad treatment benefit with daratumumab and supports its use as a potential new SOC in a cohort of patients who are considered challenging to treat.

This study has several limitations. PROs were evaluated as secondary end points and were not powered to detect differences between treatment groups. Subgroup analyses by age, ECOG PS, and depth of treatment response were post hoc. PROs were only evaluated in patients who were on treatment (patients were censored from the PRO analysis upon study treatment discontinuation) and therefore do not account for disease progression that occurred more frequently in Rd-treated patients. Additionally, patients had knowledge of their treatment assignment and both groups used active treatments, which may have influenced HRQoL responses. However, it is noteworthy that there was a clear trend for PRO improvement in favor of D-Rd over Rd across all subgroups. The PRO instruments used to measure patients' HRQoL also have limitations. The social functioning assessments of the instruments are relatively limited and may not fully capture the extent to which social functioning is impacted by the treatment regimens under investigation. For example, it is possible that the different treatment administrations (ie, infusion + oral v oral only) may have had an impact on patients' social functioning that was not assessed by the instruments used. Additionally, the EQ-5D-5L is a generic instrument and may not be as sensitive to cancer-related HRQoL changes as disease-specific questionnaires. Nevertheless, both the EORTC QLQ-C30 and EQ-5D-5L are validated instruments that are widely used to evaluate patients' overall HRQoL in the oncology setting, including in patients with MM. The statistically significant results observed in several scales further support the responsiveness of the instruments. Compliance rates with HRQoL assessments were $> 80\%$ across all time points, supporting the robustness of this data set.

In conclusion, compared with Rd, D-Rd was associated with faster and sustained clinically meaningful improvements in GHS and pain in TIE patients with NDMM regardless of age, baseline ECOG PS, or depth of treatment response. These HRQoL improvements were consistent with the clinical benefits of superior PFS and deep and durable responses observed with D-Rd and further emphasize the utility of PROs as an adjunct to clinical efficacy in the management of MM. As the treatment landscape evolves for patients with NDMM, the goals of first-line therapy should include improvement or maintenance of HRQoL reflecting clinical efficacy. Addition of daratumumab to SOC regimens supports these treatment goals in TIE patients with NDMM.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Health-Related Quality of Life in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma: Findings From the Phase III MAIA Trial**

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APPENDIX

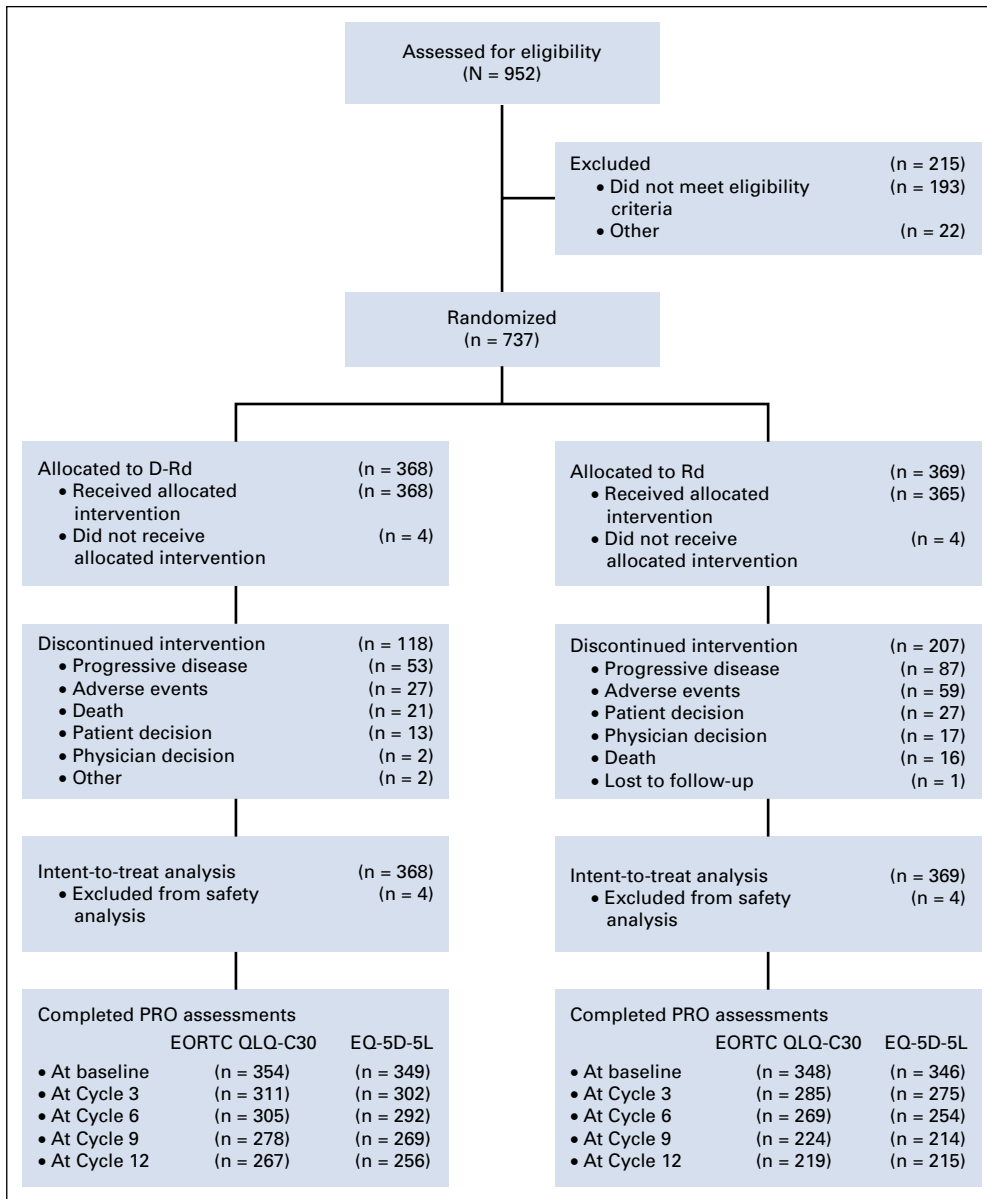


FIG A1. CONSORT Diagram.

TABLE A1. PRO Instrument Compliance Rate During Treatment (ITT Population)

PRO Instrument	D-Rd (n = 368)	Rd (n = 369)
EORTC QLQ-C30, n/N (%)		
Baseline	354/368 (96.2)	348/369 (94.3)
Cycle 3	311/348 (89.4)	285/333 (85.6)
Cycle 6	305/337 (90.5)	269/306 (87.9)
Cycle 9	278/321 (86.6)	224/273 (82.1)
Cycle 12	267/308 (86.7)	219/252 (86.9)
EQ-5D-5L, n/N (%)		
Baseline	349/368 (94.8)	346/369 (93.8)
Cycle 3	302/348 (86.8)	275/333 (82.6)
Cycle 6	292/337 (86.6)	254/306 (83.0)
Cycle 9	269/321 (83.8)	214/273 (78.4)
Cycle 12	256/308 (83.1)	215/252 (85.3)

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L, EuroQol 5-dimensional descriptive system; ITT, intent to treat; PRO, patient-reported outcome.

TABLE A2. Change From Baseline in EORTC QLQ-C30 and EQ-5D-5L VAS Scores in the ITT Population and Subgroups by Age, Baseline ECOG, and Depth of Treatment Response

LS Mean Change From Baseline (95% CI)	Cycle 3		Cycle 6		Cycle 12	
	D-Rd	Rd	D-Rd	Rd	D-Rd	Rd
EORTC QLQ-C30 global health status scores^a						
ITT population	(n = 303)	(n = 272)	(n = 295)	(n = 255)	(n = 260)	(n = 209)
	4.5 (2.4 to 6.6)	1.5 (-0.7 to 3.7)	6.4 (4.3 to 8.6)	5.6 (3.3 to 7.9)	8.4 (6.1 to 10.6)	5 (2.9 to 7.9)
< 75 years	(n = 170)	(n = 156)	(n = 168)	(n = 140)	(n = 154)	(n = 118)
	6.8 (4.1 to 9.5)	4.1 (1.3 to 7.0)	6.5 (3.7 to 9.2)	7.1 (4.2 to 10.1)	8.9 (6.1 to 11.7)	6.2 (3.0 to 9.4)
≥ 75 years	(n = 133)	(n = 116)	(n = 127)	(n = 115)	(n = 106)	(n = 91)
	1.7 (-1.3 to 4.7)	-1.8 (-5.0 to 1.4)	6.5 (3.5 to 9.6)	3.7 (0.5 to 7.0)	7.9 (4.6 to 11.2)	4.6 (1.1 to 8.2)
ECOG 0	(n = 114)	(n = 102)	(n = 113)	(n = 98)	(n = 102)	(n = 84)
	-2.6 (-5.8 to 0.6)	-4.0 (-7.4 to -0.6)	-1.4 (-4.6 to 1.9)	-1.9 (-5.4 to 1.6)	0.6 (-2.8 to 3.9)	-1.7 (-5.4 to 2.0)
ECOG 1-2	(n = 188)	(n = 170)	(n = 181)	(n = 156)	(n = 157)	(n = 124)
	8.9 (6.3 to 11.4)	5.0 (2.3 to 7.7)	11.3 (8.7 to 13.8)	10.5 (7.7 to 13.2)	13.4 (10.7 to 16.1)	9.7 (6.6 to 12.7)
≥ CR	(n = 150)	(n = 77)	(n = 155)	(n = 77)	(n = 148)	(n = 71)
	7.4 (4.3 to 10.6)	2.6 (-1.5 to 6.7)	7.4 (4.3 to 10.5)	6.7 (2.6 to 10.9)	10.2 (7.0 to 13.4)	8.7 (4.5 to 13.0)
VGPR	(n = 103)	(n = 85)	(n = 98)	(n = 88)	(n = 82)	(n = 69)
	2.2 (-1.6 to 6.0)	0.2 (-3.8 to 4.3)	6.9 (3.0 to 10.7)	5.6 (1.5 to 9.6)	10.1 (6.0 to 14.2)	4.6 (0.1 to 9.0)
≥ PR	(n = 296)	(n = 238)	(n = 291)	(n = 236)	(n = 258)	(n = 200)
	4.5 (2.4 to 6.7)	2.1 (-0.2 to 4.5)	6.4 (4.2 to 8.5)	5.9 (3.5 to 8.3)	8.4 (6.2 to 10.7)	6.2 (3.7 to 8.7)
EORTC QLQ-C30 functional scores^a						
Physical functioning						
ITT population	(n = 303)	(n = 272)	(n = 295)	(n = 255)	(n = 260)	(n = 209)
	2.4 (0.3 to 4.5)	1.7 (-0.5 to 3.9)	6.4 (4.3 to 8.6)	6.5 (4.2 to 8.8)	9.1 (6.9 to 11.3)	7.1 (4.7 to 9.5)
< 75 years	(n = 170)	(n = 156)	(n = 168)	(n = 140)	(n = 154)	(n = 118)
	3.7 (1.2 to 6.1)	3.5 (0.9 to 6.0)	6.7 (4.2 to 9.1)	8.6 (6.0 to 11.3)	9.0 (6.5 to 11.5)	8.7 (5.9 to 11.5)
≥ 75 years	(n = 133)	(n = 116)	(n = 127)	(n = 115)	(n = 106)	(n = 91)
	0.7 (-2.7 to 4.0)	-0.6 (-4.1 to 2.9)	6.0 (2.6 to 9.4)	3.7 (0.1 to 7.2)	9.3 (5.7 to 12.9)	4.9 (1.1 to 8.7)
ECOG 0	(n = 114)	(n = 102)	(n = 113)	(n = 98)	(n = 102)	(n = 84)
	-2.3 (-5.0 to 0.5)	-2.9 (-5.7 to 0)	-2.3 (-5.0 to 0.5)	-1.6 (-4.5 to 1.4)	0.8 (-2.0 to 3.7)	-1.9 (-5.0 to 1.2)
ECOG 1-2	(n = 188)	(n = 170)	(n = 181)	(n = 156)	(n = 157)	(n = 124)
	5.5 (2.7 to 8.2)	4.9 (2.0 to 7.8)	11.7 (8.9 to 14.5)	12.0 (9.0 to 15.0)	14.6 (11.7 to 17.5)	13.1 (9.9 to 16.3)
≥ CR	(n = 150)	(n = 77)	(n = 155)	(n = 77)	(n = 148)	(n = 71)
	3.3 (0.3 to 6.3)	4.1 (0.1 to 8.0)	7.9 (4.9 to 10.8)	9.5 (5.6 to 13.5)	11.6 (8.6 to 14.6)	10.8 (6.8 to 14.8)
VGPR	(n = 103)	(n = 85)	(n = 98)	(n = 88)	(n = 82)	(n = 69)
	1.5 (-2.5 to 5.6)	1.1 (-3.2 to 5.5)	6.4 (2.3 to 10.5)	7.4 (3.2 to 11.7)	8.9 (4.7 to 13.2)	7.9 (3.3 to 12.4)
≥ PR	(n = 296)	(n = 238)	(n = 291)	(n = 236)	(n = 258)	(n = 200)
	2.5 (0.3 to 4.7)	2.2 (-0.2 to 4.5)	6.5 (4.3 to 8.7)	6.8 (4.4 to 9.2)	9.1 (6.9 to 11.4)	7.7 (5.2 to 10.2)
Role functioning						
ITT population	(n = 303)	(n = 272)	(n = 295)	(n = 255)	(n = 260)	(n = 209)
	0.3 (-2.9 to 3.6)	-1.6 (-4.9 to 1.8)	7.6 (4.3 to 10.8)	5.8 (2.3 to 9.2)	11.4 (8.0 to 14.8)	9.6 (5.9 to 13.3)
< 75 years	(n = 170)	(n = 156)	(n = 168)	(n = 140)	(n = 154)	(n = 118)
	5.0 (1.2 to 8.8)	1.1 (-2.8 to 5.1)	9.1 (5.3 to 12.9)	8.5 (4.3 to 12.6)	13.1 (9.2 to 17.1)	10.1 (5.6 to 14.5)

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TABLE A2. Change From Baseline in EORTC QLQ-C30 and EQ-5D-5L VAS Scores in the ITT Population and Subgroups by Age, Baseline ECOG, and Depth of Treatment Response (continued)

LS Mean Change From Baseline (95% CI)	Cycle 3		Cycle 6		Cycle 12	
	D-Rd	Rd	D-Rd	Rd	D-Rd	Rd
≥ 75 years	(n = 133)	(n = 116)	(n = 127)	(n = 115)	(n = 106)	(n = 91)
	-6.3 (-11.3 to -1.4)	-5.7 (-11.0 to -0.4)	5.1 (0.0 to 10.2)	1.9 (-3.5 to 7.2)	8.7 (3.3 to 14.1)	8.4 (2.6 to 14.1)
ECOG 0	(n = 114)	(n = 102)	(n = 113)	(n = 98)	(n = 102)	(n = 84)
	-3.7 (-8.0 to 0.5)	-7.6 (-12.0 to -3.1)	-3.6 (-7.8 to 0.7)	-3.6 (-8.2 to 0.9)	2.9 (-1.6 to 7.3)	-0.1 (-5.0 to 4.8)
ECOG 1-2	(n = 188)	(n = 170)	(n = 181)	(n = 156)	(n = 157)	(n = 124)
	2.9 (-1.2 to 7.0)	2.8 (-1.5 to 7.1)	14.9 (10.7 to 19.0)	12.8 (8.3 to 17.2)	17.2 (12.9 to 21.6)	16.3 (11.5 to 21.2)
≥ CR	(n = 150)	(n = 77)	(n = 155)	(n = 77)	(n = 148)	(n = 71)
	0.5 (-4.1 to 5.1)	-2.9 (-9.0 to 3.2)	6.4 (1.9 to 11.0)	12.1 (6.0 to 18.2)	12.2 (7.5 to 16.8)	11.1 (4.9 to 17.4)
VGPR	(n = 103)	(n = 85)	(n = 98)	(n = 88)	(n = 82)	(n = 69)
	-0.7 (-6.4 to 4.9)	-2.6 (-8.6 to 3.5)	9.9 (4.1 to 15.6)	3.4 (-2.6 to 9.4)	13.9 (7.8 to 20.0)	10.7 (4.1 to 17.2)
≥ PR	(n = 296)	(n = 238)	(n = 291)	(n = 236)	(n = 258)	(n = 200)
	0.5 (-2.8 to 3.7)	-1.6 (-5.2 to 1.9)	7.9 (4.7 to 11.2)	6.2 (2.6 to 9.8)	11.3 (7.9 to 14.7)	10.1 (6.3 to 13.9)
Emotional functioning						
ITT population	(n = 303)	(n = 272)	(n = 295)	(n = 255)	(n = 260)	(n = 209)
	7.1 (4.9 to 9.4)	5.0 (2.6 to 7.3)	6.7 (4.4 to 9.0)	4.8 (2.4 to 7.3)	9.5 (7.1 to 11.9)	6.4 (3.8 to 9.0)
< 75 years	(n = 170)	(n = 156)	(n = 168)	(n = 140)	(n = 154)	(n = 118)
	7.1 (4.2 to 9.9)	6.8 (3.9 to 9.8)	4.9 (2.1 to 7.8)	6.1 (3.0 to 9.2)	8.3 (5.3 to 11.2)	6.7 (3.4 to 10.0)
≥ 75 years	(n = 133)	(n = 116)	(n = 127)	(n = 115)	(n = 106)	(n = 91)
	5.2 (1.8 to 8.5)	0.6 (-2.9 to 4.1)	6.9 (3.5 to 10.3)	1.3 (-2.3 to 4.8)	9.1 (5.5 to 12.7)	4.0 (0.2 to 7.9)
ECOG 0	(n = 114)	(n = 102)	(n = 113)	(n = 98)	(n = 102)	(n = 84)
	2.1 (-1.1 to 5.3)	2.6 (-0.8 to 6.0)	1.2 (-2.0 to 4.4)	0.3 (-3.1 to 3.8)	2.3 (-1.0 to 5.6)	0.4 (-3.2 to 4.0)
ECOG 1-2	(n = 188)	(n = 170)	(n = 181)	(n = 156)	(n = 157)	(n = 124)
	8.9 (6.1 to 11.7)	5.4 (2.5 to 8.4)	8.7 (5.9 to 11.6)	6.7 (3.6 to 9.7)	12.8 (9.8 to 15.8)	9.0 (5.7 to 12.3)
≥ CR	(n = 150)	(n = 77)	(n = 155)	(n = 77)	(n = 148)	(n = 71)
	7.2 (4.0 to 10.4)	7.9 (3.7 to 12.1)	7.9 (4.7 to 11.1)	6.2 (2.0 to 10.4)	9.8 (6.5 to 13.0)	9.1 (4.7 to 13.4)
VGPR	(n = 103)	(n = 85)	(n = 98)	(n = 88)	(n = 82)	(n = 69)
	8.6 (4.5 to 12.7)	2.4 (-1.9 to 6.8)	6.9 (2.8 to 11.1)	4.7 (0.3 to 9.0)	12.3 (7.9 to 16.7)	6.2 (1.4 to 10.9)
≥ PR	(n = 296)	(n = 238)	(n = 291)	(n = 236)	(n = 258)	(n = 200)
	7.2 (4.9 to 9.5)	5.4 (2.9 to 7.9)	6.9 (4.6 to 9.2)	4.8 (2.3 to 7.4)	9.7 (7.2 to 12.1)	7.1 (4.4 to 9.7)
Cognitive functioning						
ITT population	(n = 303)	(n = 272)	(n = 295)	(n = 254)	(n = 260)	(n = 209)
	-0.3 (-2.5 to 2.0)	0.4 (-1.9 to 2.7)	-1.9 (-4.2 to 0.3)	-0.7 (-3.1 to 1.6)	-1.5 (-3.8 to 0.9)	-0.7 (-3.2 to 1.9)
< 75 years	(n = 170)	(n = 156)	(n = 168)	(n = 140)	(n = 154)	(n = 118)
	0.9 (-1.8 to 3.7)	2.5 (-0.4 to 5.3)	-3.3 (-6.1 to -0.6)	-0.8 (-3.8 to 2.2)	-3.3 (-6.1 to -0.4)	-1.0 (-4.2 to 2.2)
≥ 75 years	(n = 133)	(n = 116)	(n = 127)	(n = 114)	(n = 106)	(n = 91)
	-1.5 (-4.7 to 1.7)	-1.8 (-5.2 to 1.6)	0.1 (-3.1 to 3.4)	-0.1 (-3.6 to 3.3)	1.4 (-2.1 to 4.9)	0.4 (-3.3 to 4.1)
ECOG 0	(n = 114)	(n = 102)	(n = 113)	(n = 98)	(n = 102)	(n = 84)
	-2.2 (-5.2 to 0.8)	1.0 (-2.3 to 4.2)	-6.2 (-9.2 to -3.1)	-1.8 (-5.1 to 1.4)	-6.5 (-9.7 to -3.4)	-4.1 (-7.5 to -0.6)
ECOG 1-2	(n = 188)	(n = 170)	(n = 181)	(n = 155)	(n = 157)	(n = 124)
	0.9 (-1.9 to 3.7)	0.3 (-2.6 to 3.3)	0.8 (-2.0 to 3.7)	0.3 (-2.7 to 3.4)	2.0 (-1.0 to 5.0)	2.1 (-1.3 to 5.4)

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TABLE A2. Change From Baseline in EORTC QLQ-C30 and EQ-5D-5L VAS Scores in the ITT Population and Subgroups by Age, Baseline ECOG, and Depth of Treatment Response (continued)

LS Mean Change From Baseline (95% CI)	Cycle 3		Cycle 6		Cycle 12	
	D-Rd	Rd	D-Rd	Rd	D-Rd	Rd
≥ CR	(n = 150) -0.1 (-3.6 to 3.3)	(n = 77) 1.4 (-3.1 to 5.9)	(n = 155) -1.1 (-4.5 to 2.3)	(n = 77) -1.2 (-5.7 to 3.3)	(n = 148) -0.7 (-4.2 to 2.7)	(n = 71) -0.4 (-5.1 to 4.2)
VGPR	(n = 103) 0.9 (-3.1 to 4.8)	(n = 85) -3.0 (-7.2 to 1.2)	(n = 98) -2.6 (-6.6 to 1.5)	(n = 88) -1.5 (-5.7 to 2.7)	(n = 82) -1.3 (-5.5 to 3.0)	(n = 69) -0.9 (-5.5 to 3.6)
≥ PR	(n = 296) -0.2 (-2.5 to 2.0)	(n = 238) 0.2 (-2.2 to 2.7)	(n = 291) -2.0 (-4.3 to 0.3)	(n = 235) -0.8 (-3.3 to 1.7)	(n = 258) -1.5 (-3.9 to 0.9)	(n = 200) -0.5 (-3.2 to 2.1)
Social functioning						
ITT population	(n = 303) -0.8 (-3.6 to 2.0)	(n = 272) -0.0 (-2.9 to 2.9)	(n = 295) 4.0 (1.2 to 6.9)	(n = 254) 2.5 (-0.5 to 5.4)	(n = 260) 7.9 (5.0 to 10.8)	(n = 209) 5.3 (2.1 to 8.4)
< 75 years	(n = 170) 2.8 (-0.6 to 6.1)	(n = 156) 2.7 (-0.8 to 6.3)	(n = 168) 7.8 (4.4 to 11.2)	(n = 140) 6.4 (2.7 to 10.0)	(n = 154) 10.0 (6.5 to 13.5)	(n = 118) 7.9 (4.0 to 11.8)
≥ 75 years	(n = 133) -5.4 (-9.6 to -1.2)	(n = 116) -3.7 (-8.1 to 0.8)	(n = 127) -0.9 (-5.2 to 3.4)	(n = 114) -2.5 (-7.1 to 2.0)	(n = 106) 5.4 (0.8 to 9.9)	(n = 91) 1.8 (-3.0 to 6.7)
ECOG 0	(n = 114) -5.7 (-9.3 to -2.1)	(n = 102) -4.6 (-8.4 to -0.7)	(n = 113) -5.7 (-9.3 to -2.0)	(n = 98) -4.7 (-8.5 to -0.8)	(n = 102) -0.9 (-4.7 to 2.9)	(n = 84) -3.4 (-7.5 to 0.7)
ECOG 1-2	(n = 188) 2.9 (-0.7 to 6.4)	(n = 170) 3.2 (-0.5 to 7.0)	(n = 181) 10.4 (6.8 to 14.0)	(n = 155) 7.5 (3.6 to 11.4)	(n = 157) 14.2 (10.4 to 18.0)	(n = 124) 11.0 (6.8 to 15.3)
≥ CR	(n = 150) 0.7 (-3.4 to 4.7)	(n = 77) 4.6 (-0.7 to 9.9)	(n = 155) 7.2 (3.2 to 11.2)	(n = 77) 7.1 (1.8 to 12.4)	(n = 148) 10.5 (6.4 to 14.5)	(n = 71) 7.5 (2.0 to 13.0)
VGPR	(n = 103) -2.0 (-7.0 to 3.1)	(n = 85) -4.0 (-9.4 to 1.4)	(n = 98) 2.6 (-2.6 to 7.7)	(n = 88) 0.4 (-5.0 to 5.7)	(n = 82) 8.4 (3.0 to 13.9)	(n = 69) 3.2 (-2.6 to 9.0)
≥ PR	(n = 296) -0.7 (-3.6 to 2.1)	(n = 238) 0.3 (-2.7 to 3.4)	(n = 291) 4.1 (1.3 to 7.0)	(n = 235) 2.6 (-0.5 to 5.7)	(n = 258) 7.9 (4.9 to 10.8)	(n = 200) 5.7 (2.5 to 9.0)
EORTC QLQ-C30 symptom scores ^b						
Pain						
ITT population	(n = 303) -17.9 (-20.7 to -15.0)	(n = 272) -11.0 (-14.0 to -8.1)	(n = 295) -18.0 (-20.9 to -15.1)	(n = 255) -14.1 (-17.1 to -11.0)	(n = 260) -17.3 (-20.3 to -14.2)	(n = 209) -14.9 (-18.3 to -11.6)
< 75 years	(n = 170) -19.2 (-22.6 to -15.8)	(n = 156) -13.0 (-16.6 to -9.5)	(n = 168) -17.1 (-20.5 to -13.6)	(n = 140) -16.2 (-19.9 to -12.5)	(n = 154) -18.1 (-21.6 to -14.6)	(n = 118) -16.5 (-20.4 to -12.5)
≥ 75 years	(n = 133) -14.8 (-19.2 to -10.3)	(n = 116) -7.2 (-12.0 to -2.5)	(n = 127) -17.9 (-22.4 to -13.3)	(n = 115) -10.0 (-14.8 to -5.2)	(n = 106) -14.9 (-19.7 to 10.0)	(n = 91) -11.6 (-16.9 to -6.4)
ECOG 0	(n = 114) -10.3 (-14.2 to -6.5)	(n = 102) -3.9 (-7.9 to 0.2)	(n = 113) -7.5 (-11.3 to -3.6)	(n = 98) -3.0 (-7.1 to 1.1)	(n = 102) -6.0 (-10.0 to -2.0)	(n = 84) -2.2 (-6.6 to 2.2)
ECOG 1-2	(n = 188) -22.1 (-25.8 to -18.3)	(n = 170) -15.1 (-19.0 to -11.1)	(n = 181) -23.8 (-27.6 to -20.0)	(n = 156) -20.6 (-24.7 to -16.6)	(n = 157) -23.9 (-27.9 to -19.9)	(n = 124) -22.0 (-26.5 to -17.5)
≥ CR	(n = 150) -18.2 (-22.4 to -13.9)	(n = 77) -15.8 (-21.3 to -10.2)	(n = 155) -19.2 (-23.4 to -15.0)	(n = 77) -16.4 (-22.0 to -10.8)	(n = 148) -18.3 (-22.6 to -14.1)	(n = 71) -18.0 (-23.7 to -12.2)

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TABLE A2. Change From Baseline in EORTC QLQ-C30 and EQ-5D-5L VAS Scores in the ITT Population and Subgroups by Age, Baseline ECOG, and Depth of Treatment Response (continued)

LS Mean Change From Baseline (95% CI)	Cycle 3		Cycle 6		Cycle 12	
	D-Rd	Rd	D-Rd	Rd	D-Rd	Rd
VGPR	(n = 103)	(n = 85)	(n = 98)	(n = 88)	(n = 82)	(n = 69)
	-18.9 (-24.1 to -13.7)	-5.0 (-10.5 to 0.6)	-17.9 (-23.3 to -12.6)	-12.2 (-17.8 to -6.7)	-17.5 (-23.1 to -11.9)	-13.7 (-19.7 to -7.7)
≥ PR	(n = 296)	(n = 238)	(n = 291)	(n = 236)	(n = 258)	(n = 200)
	-18.0 (-20.9 to -15.1)	-11.0 (-14.2 to -7.8)	-18.0 (-21.0 to -15.1)	-14.3 (-17.5 to -11.1)	-17.1 (-20.1 to -14.0)	-15.2 (-18.6 to -11.7)
Fatigue						
ITT population	(n = 303)	(n = 272)	(n = 295)	(n = 255)	(n = 260)	(n = 209)
	-0.2 (-2.9 to 2.4)	1.8 (-0.9 to 4.6)	-2.2 (-4.9 to 0.4)	-3.0 (-5.8 to -0.2)	-5.5 (-8.3 to -2.7)	-2.9 (-6.0 to 0.1)
< 75 years	(n = 170)	(n = 156)	(n = 168)	(n = 140)	(n = 154)	(n = 118)
	-1.6 (-4.8 to 1.6)	1.5 (-1.9 to 4.8)	-2.1 (-5.3 to 1.1)	-2.7 (-6.2 to 0.7)	-5.8 (-9.1 to -2.5)	-3.4 (-7.1 to 0.3)
≥ 75 years	(n = 133)	(n = 116)	(n = 127)	(n = 115)	(n = 106)	(n = 91)
	2.4	3.1	-1.5	-2.4	-4.2	-1.2
	(-1.6 to 6.5)	(-1.2 to 7.3)	(-5.6 to 2.6)	(-6.7 to 1.9)	(-8.6 to 0.1)	(-5.8 to 3.4)
ECOG 0	(n = 114)	(n = 102)	(n = 113)	(n = 98)	(n = 102)	(n = 84)
	6.0 (2.2 to 9.7)	7.5 (3.5 to 11.4)	8.5 (4.8 to 12.3)	7.1 (3.1 to 11.1)	4.9 (1.0 to 8.8)	7.0 (2.7 to 11.2)
ECOG 1-2	(n = 188)	(n = 170)	(n = 181)	(n = 156)	(n = 157)	(n = 124)
	-3.5 (-6.8 to -0.3)	-1.3 (-4.7 to 2.1)	-8.0 (-11.3 to -4.7)	-8.9 (-12.4 to -5.4)	-11.5 (-14.9 to -8.0)	-8.7 (-12.5 to -4.9)
≥ CR	(n = 150)	(n = 77)	(n = 155)	(n = 77)	(n = 148)	(n = 71)
	-0.5 (-4.2 to 3.3)	-3.1 (-8.0 to 1.9)	-2.1 (-5.8 to 1.6)	-7.6 (-12.5 to -2.6)	-5.4 (-9.1 to -1.6)	-5.9 (-11.0 to -0.8)
VGPR	(n = 103)	(n = 85)	(n = 98)	(n = 88)	(n = 82)	(n = 69)
	0.6 (-4.3 to 5.5)	6.7 (1.5 to 11.9)	-2.5 (-7.5 to 2.4)	0.2 (-5.0 to 5.3)	-6.7 (-11.9 to -1.5)	-2.8 (-8.4 to 2.8)
≥ PR	(n = 296)	(n = 238)	(n = 291)	(n = 236)	(n = 258)	(n = 200)
	-0.2 (-2.9 to 2.5)	1.2 (-1.8 to 4.1)	-2.2 (-4.9 to 0.5)	-3.0 (-6.0 to -0.0)	-5.5 (-8.3 to -2.7)	-3.7 (-6.8 to -0.6)
Nausea or vomiting						
ITT population	(n = 303)	(n = 272)	(n = 295)	(n = 255)	(n = 260)	(n = 209)
	0.6 (-1.0 to 2.2)	2.2 (0.5 to 3.9)	-1.5 (-3.1 to 0.1)	-1.2 (-3.0 to 0.5)	-4.0 (-5.7 to -2.3)	-1.9 (-3.8 to -0.1)
< 75 years	(n = 170)	(n = 156)	(n = 168)	(n = 140)	(n = 154)	(n = 118)
	1.5 (-0.5 to 3.6)	1.4 (-0.7 to 3.5)	-1.4 (-3.5 to 0.7)	-1.4 (-3.6 to 0.9)	-3.4 (-5.5 to -1.2)	-3.0 (-5.4 to -0.6)
≥ 75 years	(n = 133)	(n = 116)	(n = 127)	(n = 115)	(n = 106)	(n = 91)
	0.6 (-1.7 to 2.9)	4.4 (1.9 to 6.9)	-0.4 (-2.7 to 2.0)	0.1 (-2.4 to 2.6)	-3.6 (-6.1 to -1.0)	0.6 (-2.2 to 3.3)
ECOG 0	(n = 114)	(n = 102)	(n = 113)	(n = 98)	(n = 102)	(n = 84)
	0.9 (-1.2 to 2.9)	2.9 (0.7 to 5.0)	0.3 (-1.7 to 2.3)	0.5 (-1.6 to 2.7)	-2.0 (-4.1 to 0.1)	0.9 (-1.4 to 3.2)
ECOG 1-2	(n = 188)	(n = 170)	(n = 181)	(n = 156)	(n = 157)	(n = 124)
	1.4 (-0.6 to 3.4)	2.6 (0.5 to 4.7)	-1.9 (-3.9 to 0.2)	-1.4 (-3.6 to 0.8)	-4.7 (-6.8 to -2.5)	-2.8 (-5.2 to -0.4)
≥ CR	(n = 150)	(n = 77)	(n = 155)	(n = 77)	(n = 148)	(n = 71)
	0.8 (-1.6 to 3.2)	0.4 (-2.7 to 3.5)	-3.2 (-5.6 to -0.9)	-3.6 (-6.7 to -0.5)	-5.2 (-7.6 to -2.8)	-1.6 (-4.9 to 1.6)
VGPR	(n = 103)	(n = 85)	(n = 98)	(n = 88)	(n = 82)	(n = 69)
	1.7 (-1.1 to 4.5)	6.7 (3.7 to 9.8)	0.1 (-2.8 to 3.0)	-0.1 (-3.1 to 2.9)	-3.4 (-6.5 to -0.4)	-1.7 (-5.1 to 1.6)
≥ PR	(n = 296)	(n = 238)	(n = 291)	(n = 236)	(n = 258)	(n = 200)
	0.8 (-0.9 to 2.4)	2.7 (0.9 to 4.5)	-1.3 (-3.0 to 0.3)	-0.9 (-2.8 to 0.9)	-3.9 (-5.6 to -2.2)	-1.7 (-3.6 to 0.3)

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TABLE A2. Change From Baseline in EORTC QLQ-C30 and EQ-5D-5L VAS Scores in the ITT Population and Subgroups by Age, Baseline ECOG, and Depth of Treatment Response (continued)

LS Mean Change From Baseline (95% CI)	Cycle 3		Cycle 6		Cycle 12	
	D-Rd	Rd	D-Rd	Rd	D-Rd	Rd
EQ-5D-5L						
VAS ^a						
ITT population	(n = 290)	(n = 262)	(n = 280)	(n = 240)	(n = 247)	(n = 206)
	4.9 (3.0 to 6.7)	2.5 (0.6 to 4.4)	8.0 (6.1 to 9.8)	5.7 (3.7 to 7.7)	10.1 (8.1 to 12.1)	4.9 (2.8 to 7.0)
< 75 years	(n = 161)	(n = 150)	(n = 161)	(n = 132)	(n = 146)	(n = 116)
	4.2 (1.9 to 6.5)	2.1 (-0.4 to 4.5)	6.0 (3.6 to 8.3)	5.4 (2.8 to 7.9)	9.2 (6.8 to 11.6)	4.6 (1.9 to 7.3)
≥ 75 years	(n = 129)	(n = 112)	(n = 119)	(n = 108)	(n = 101)	(n = 90)
	3.1 (0.3 to 5.9)	0.5 (-2.5 to 3.4)	8.2 (5.3 to 11.1)	3.6 (0.6 to 6.7)	9.1 (6.0 to 12.1)	2.8 (-0.5 to 6.0)
ECOG 0	(n = 109)	(n = 99)	(n = 106)	(n = 90)	(n = 99)	(n = 83)
	-2.7 (-5.5 to 0.1)	-3.8 (-6.7 to -0.8)	-0.1 (-2.9 to 2.7)	-2.6 (-5.7 to 0.4)	0.4 (-2.6 to 3.3)	-4.8 (-8.0 to -1.6)
ECOG 1-2	(n = 180)	(n = 163)	(n = 173)	(n = 149)	(n = 147)	(n = 122)
	7.9 (5.6 to 10.2)	4.9 (2.5 to 7.3)	11.5 (9.1 to 13.8)	9.6 (7.1 to 12.1)	14.8 (12.3 to 17.3)	9.6 (6.9 to 12.3)
≥ CR	(n = 143)	(n = 76)	(n = 148)	(n = 72)	(n = 138)	(n = 71)
	6.1 (3.3 to 8.9)	2.7 (-0.9 to 6.3)	8.4 (5.6 to 11.1)	7.7 (4.0 to 11.4)	11.3 (8.6 to 14.1)	8.9 (5.2 to 12.6)
VGPR	(n = 98)	(n = 81)	(n = 92)	(n = 85)	(n = 80)	(n = 68)
	3.6 (0.3 to 6.8)	-0.1 (-3.6 to 3.4)	6.8 (3.4 to 10.1)	4.5 (1.0 to 8.0)	11.3 (7.8 to 14.8)	1.5 (-2.3 to 5.3)
≥ PR	(n = 283)	(n = 231)	(n = 276)	(n = 221)	(n = 245)	(n = 197)
	4.9 (3.0 to 6.8)	2.4 (0.3 to 4.4)	8.0 (6.1 to 9.9)	6.1 (4.0 to 8.2)	10.2 (8.2 to 12.1)	5.3 (3.1 to 7.4)

Abbreviations: CR, complete response; D-Rd, daratumumab, lenalidomide, and dexamethasone; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L, EuroQol 5-dimensional descriptive system; GHS, global health status; ITT, intent to treat; LS, least squares; PR, partial response; Rd, lenalidomide and dexamethasone; VAS, visual analog scale; VGPR, very good partial response.

^aA positive change equates to greater symptom improvement.

^bA negative change equates to greater symptom improvement.