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Quality of life is maintained with ixazomib maintenance in post-transplant newly diagnosed multiple myeloma: The TOURMALINE-MM3 trial

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Abstract

Objectives: Health-related quality of life (HRQoL) is particularly important during maintenance therapy (MT) in newly diagnosed multiple myeloma post-transplant, when disease symptoms are limited.

Methods: We assessed HRQoL in patients randomised to 26 cycles of MT (ixazomib vs placebo) in TOURMALINE-MM3 (NCT02181413).

Results: The characteristics at study entry were well-balanced between ixazomib (n = 386) and placebo (n = 251) arms. At study entry, EORTC QLQ-C30 and MY20 scores were high for functional scales and low for symptom scales and were comparable with those of the general population. Changes in subscale scores across intervals, analysed over 30 four-week intervals using a linear mixed-effects model, were generally small and similar between arms for the EORTC QLQ-C30 Global Health Status/QoL, Physical Functioning, and Pain subscales and EORTC QLQ-MY20

Disease Symptoms subscale and Peripheral Neuropathy item. EORTC QLQ-C30 Nausea/Vomiting and Diarrhoea subscales were consistently worse for ixazomib than for placebo, in line with the ixazomib toxicity profile. Even when least-squares mean differences between arms were statistically significant, none reached the established minimal important clinical difference of 10 in multiple myeloma.

Conclusions: In addition to improvement in progression-free survival with ixazomib, HRQoL was maintained in both arms. Active treatment with ixazomib did not have an adverse impact on HRQoL.

KEYWORDS

HRQoL, ixazomib, maintenance, placebo-controlled, TOURMALINE-MM3

1 | INTRODUCTION

Multiple myeloma (MM), the second most common haematologic malignancy, is incurable despite therapeutic advances. Recent years have witnessed improvements in survival with the routine use of high-dose therapy and autologous stem cell transplant (ASCT), the introduction of novel therapies and improved supportive care.[1] Following ASCT, maintenance therapy (MT) is administered to induce long-term disease control to maximise progression-free survival (PFS) for patients with MM.[2,3] Because maintenance therapies for MM are intended for administration over a long period, potentially for many years, their tolerability, toxicity and impact on health-related quality of life (HRQoL) are important factors to consider in treatment decision making.[3] In clinical practice, the most commonly administered post-ASCT MT is the immunomodulator lenalidomide, which is the only agent approved for this use, followed by the proteasome inhibitor bortezomib (used off label in this setting).[4-6] Lenalidomide is associated with adverse events (AEs) including cytopenia, secondary malignancy, and dermatologic and gastrointestinal toxicities,[5] whereas bortezomib is associated with peripheral neuropathy. Discontinuations related to toxicity or patient-convenience issues are common with these treatments in routine care, occurring in 17%-29% of patients treated with lenalidomide and 7%-20% of patients treated with bortezomib.[4,5,7-9]

We could not identify any trial-based analyses of HRQoL among patients treated with lenalidomide or bortezomib MT in the post-ASCT setting; however, other limited trial evidence suggests that some maintenance regimens (eg thalidomide-prednisone) may negatively affect HRQoL, potentially due to side effects.[10] Post-ASCT MT in MM, given when disease burden is minimal, aims to delay disease progression without adverse effects of cancer treatment; thus, HRQoL is of particular importance in this setting.[2] Nevertheless, the impact on HRQoL of maintenance treatment for patients with MM is not well understood.[11,12]

Ixazomib is an oral proteasome inhibitor currently indicated in combination with lenalidomide and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. The phase 3 placebo-controlled, double-blind TOURMALINE-MM3 study investigated ixazomib as a MT following ASCT in adult patients newly diagnosed with MM. Single-agent oral ixazomib as a MT resulted in a statistically significant improvement in PFS relative to placebo.[13] In addition, TOURMALINE-MM3 was the first trial of maintenance therapies currently used in clinical practice to assess the impact of MT on HRQoL after ASCT in patients with newly diagnosed MM. Subjects' HRQoL was evaluated using two patient-reported European Organisation for Research and Treatment of Cancer (EORTC) questionnaires: the general EORTC Quality of Life Questionnaire Core Module 30

Novelty statements

- *What is the NEW aspect of your work? (ONE sentence).* Because the impact of maintenance treatment on health-related quality of life (HRQoL) for patients with newly diagnosed multiple myeloma (MM) after autologous stem cell transplant is not well understood, this analysis aimed to assess, in detail, the impact of ixazomib therapy compared with placebo on HRQoL, patient-reported MM-specific symptoms and functioning in the phase 3 placebo-controlled, double-blind TOURMALINE-MM3 trial.
- *What is the CENTRAL finding of your work? (ONE sentence).* Active treatment with ixazomib did not have an adverse impact on HRQoL, and the high level of functioning and minimal disease burden patients exhibited at study entry were maintained during maintenance treatment.
- *What is (or could be) the SPECIFIC clinical relevance of your work?* Ixazomib is a uniquely suited treatment option that fulfils the goals of maintenance therapy—prolonging progression-free survival, exhibiting no adverse impact on HRQoL and offering a favourable toxicity profile—and should be considered for maintenance therapy after autologous stem cell transplant in individuals with newly diagnosed MM.

(QLQ-C30) and the MM-specific EORTC QLQ-Multiple Myeloma Module 20 (QLQ-MY20). No difference was observed between the treatment groups in the global health domain (Global Health Status/QoL) of the EORTC QLQ-C30, which was reported as a secondary objective in the main study.[13]

The aim of this analysis was to assess, in detail, the impact of ixazomib therapy compared with placebo on HRQoL, patient-reported MM-specific symptoms and functioning in TOURMALINE-MM3 in the context of an established minimal important difference (MID), or the smallest change in a patient-reported outcome (PRO) measure considered important to patients.[14-16] Of particular interest were the domains and items considered most clinically relevant and likely to be impacted by MM and/or MT: Global Health Status/QoL, Physical Functioning, Role Functioning, Pain, Nausea/Vomiting and Diarrhoea subscales from the EORTC QLQ-C30 plus Disease Symptoms subscale and Peripheral Neuropathy item from the EORTC QLQ-MY20.[17,18]

2 | METHODS

2.1 | Study design

The design and primary results of the phase 3, double-blind, placebo-controlled TOURMALINE-MM3 trial (NCT02181413) have been reported previously.[13] Briefly, eligible participants were adults with at least a partial response after induction therapy followed by high-dose melphalan conditioning and a single ASCT within 12 months of diagnosis. The induction regimen must have included a proteasome inhibitor or an immunomodulatory drug. An Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 was required for study eligibility. Patients were randomly assigned in a 3:2 ratio to MT with oral ixazomib or placebo on days 1, 8 and 15 in 4-week cycles for 26 cycles. Patients, investigators and study staff were blinded to treatment allocation. Patients could discontinue MT at disease progression or if they experienced unacceptable toxicity, and were not allowed to re-enter the study. Among 393 patients who received ixazomib, 194 (49.4%) discontinued treatment; reasons for discontinuation were progressive disease (n = 143, 36.4%), AE (n = 24, 6.1%), withdrawal of consent (n = 7, 1.8%) and other (n = 20, 5.1%). Among 260 patients who received placebo, 151 (58.1%) discontinued treatment; reasons for discontinuation were progressive disease (n = 121, 46.5%), AE (n = 7, 2.7%), withdrawal of consent (n = 4, 1.5%) and other (n = 19, 7.3%).[13]

2.2 | Patient-reported outcome measures

Subjects' HRQoL and MM-specific symptoms were evaluated as secondary or exploratory endpoints in TOURMALINE-MM3 using two patient-reported EORTC questionnaires. In prespecified analyses, HRQoL was evaluated using the EORTC QLQ-C30, a 30-item self-reported measure of health status, functioning and symptoms among individuals with cancer participating in clinical trials. The EORTC QLQ-C30 is based on a 1-week recall and includes 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning and Social Functioning), 1 Global Health Status/QoL scale, 3 symptom scales (Fatigue, Nausea/Vomiting and Pain) and 6 single items (Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea and Financial Difficulties).[19] An EORTC QLQ-C30 summary score is calculated from the mean of 13 of the 15 subscales (Global Health Status/QoL and Financial Difficulties scales are excluded).[20] The EORTC QLQ-C30 has demonstrated reliability and validity among patients with MM.[21]

MM-specific symptoms were assessed by the EORTC QLQ-MY20, a 20-item self-reported measure of the functional and symptom impact of MM, administered in conjunction with the EORTC QLQ-C30. The EORTC QLQ-MY20 is also based on a 1-week recall and includes 2 functional subscales (Body Image, Future Perspective) and 2 symptoms scales (Disease Symptoms [6 items, including pain] and Side Effects of Treatment [10 items, including peripheral neuropathy]). The EORTC QLQ-MY20 has demonstrated reliability and validity among patients with MM.[22] EORTC QLQ-MY20 subscales were evaluated in prespecified analyses; in addition, given the clinical relevance of peripheral neuropathy, we also conducted post hoc analyses on this single item from the Side Effects of Treatment subscale. The raw score was first standardised to range from 0 to 100, where a higher score indicates a high level of symptomatology/problems.

Subscale scores on both measures and the summary score of the EORTC QLQ-C30 range from 0 to 100. For both measures, higher scores for the summary, global and functional domains indicate better HRQoL, while higher scores on symptom scales represent higher levels of symptomatology. Treatment differences were interpreted in the context of an established minimal important difference (MID) of 10 on the EORTC QLQ-C30 in MM.[15,16] An MID is the smallest change in a patient-reported outcome (PRO) measure considered important to patients.[14] After reviewing the literature, we found no established MIDs for the EORTC QLQ-MY20. Stewart et al[10] calculated the standard error of measurement (SEM) for EORTC QLQ-MY20 baseline subscale scores from the ASPIRE trial in relapsed MM, with estimates ranging from 7 to 11. Therefore, a value of 10 points was chosen as a reasonable threshold for the EORTC QLQ-MY20 analyses.

The EORTC QLQ-C30 was administered at screening (study days −15 to −1 prior to initiation of protocol therapy), the start of every cycle[1-26], end of treatment, every 4 weeks until start of next line of therapy after progression and twice thereafter. The EORTC QLQ-MY20 was administered at screening, the start of every 3 cycles between cycles 1 and 25, end of treatment, every 4 weeks until start of next line of therapy after progression and twice thereafter.

2.3 | Statistical analyses

Compliance was measured in the intent-to-treat population. At each scheduled visit, compliance with HRQoL assessments was defined as the number of assessment forms received divided by the number of forms expected (ie from patients who were alive and still on study). Overall compliance was defined as the total

TABLE 1 Baseline patient characteristics

	Placebo N = 251	Ixazomib N = 386	Total N = 637
Age (y)[a]			
Median (IQR)	60 (54-64)	58 (52-63)	58 (52-64)
<60 y	123 (49)	223 (58)	346 (54)
60-<75 y	128 (51)	163 (42)	291 (46)
Sex n (%)			
Male	156 (62)	247 (64)	403 (63)
Female	95 (38)	139 (36)	234 (37)
Race n (%)			
White	204 (81)	306 (79)	510 (80)
Black or African American	2 (<1)	7 (2)	9 (1)
Asian	36 (14)	59 (15)	95 (15)
Other or not reported	9 (<4)	14 (4)	23 (4)
Type of myeloma at initial diagnosis n (%)			
IgG	142 (57)	224 (58)	366 (57)
IgA	58 (23)	86 (22)	144 (23)
IgD	3 (1)	8 (2)	11 (2)
IgM	0	3 (<1)	3 (<1)
Biclonal	3 (1)	1 (<1)	4 (<1)
Light chain (no heavy chain)	44 (18)	62 (16)	106 (17)
Unknown	1 (<1)	2 (<1)	3 (<1)
ISS stage at initial diagnosis, n (%)			
I	91 (36)	146 (38)	237 (37)
II	89 (35)	129 (33)	218 (34)
III	71 (28)	111 (29)	182 (29)
ECOG performance status at study entry,[b] n (%)			
0	171 (68)	250 (65)	421 (66)
1	74 (29)	125 (32)	199 (31)
2	5 (2)	11 (3)	16 (3)
Missing	1	0	1
Creatinine clearance[c] at study entry[b] (mL/min), n (%)			
≥30 and < 60	18 (7)	38 (10)	56 (9)
≥60 and < 90	79 (31)	98 (25)	177 (28)
≥90	154 (61)	250 (65)	404 (63)
Cytogenetic risk category,[d] n (%)			
High-risk group	50 (20)	61 (16)	111 (17)
Standard risk	149 (59)	244 (63)	393 (62)
Unclassifiable	52 (21)	81 (21)	133 (21)
Induction regimen			
PI without IMiD	153 (61)	226 (59)	379 (59)
IMiD without PI	26 (10)	43 (11)	69 (11)
IMiD and PI	72 (29)	117 (30)	189 (30)
Response after ASCT by PI at study entry[b]			
sCR	51 (20)	67 (17)	118 (19)
CR	36 (14)	61 (16)	97 (15)
VGPR	111 (44)	177 (46)	288 (45)
PR	53 (21)	81 (21)	134 (21)

(Continues)

TABLE 1 (Continued)

	Placebo N = 251	Ixazomib N = 386	Total N = 637
Time since initial diagnosis to first dose of study treatment[e] (mo)			
N	251	386	637
Mean (SD)	10.0 (3.58)	10.4 (4.79)	10.2 (4.36)
Median	9.3	9.5	9.5
Min, Max	5, 55	6, 70	5, 70
Time since ASCT to first dose of study treatment[f] (mo)			
N	251	386	637
Mean (SD)	3.3 (0.30)	3.4 (0.34)	3.4 (0.33)
Median	3.4	3.4	3.4
Min, Max	3, 5	3, 6	3, 6
EORTC QLQ-C30 scores at study entry,[b,g] mean (SD)			
Global Health Status/QoL	70.4 (16.67)	71.0 (18.35)	70.7 (17.69)
Physical functioning	81.3 (17.32)	81.3 (18.62)	81.3 (18.10)
Role functioning	73.2 (25.90)	73.2 (28.56)	73.2 (27.52)
Emotional functioning	83.4 (19.31)	85.2 (19.39)	84.5 (19.36)
Cognitive functioning	89.2 (15.60)	88.3 (17.92)	88.7 (17.04)
Social functioning	80.1 (22.13)	78.7 (25.84)	79.3 (24.44)
Fatigue	24.9 (19.98)	26.0 (21.11)	25.6 (20.66)
Pain	23.8 (24.84)	23.4 (24.34)	23.5 (24.52)
Nausea/Vomiting	2.9 (10.52)	3.2 (9.58)	3.0 (9.95)
Dyspnoea	11.7 (19.68)	13.1 (19.68)	12.6 (19.67)
Insomnia	18.9 (25.96)	17.3 (26.45)	17.9 (26.25)
Appetite loss	8.8 (19.62)	9.0 (19.96)	8.9 (19.81)
Constipation	6.2 (16.89)	7.1 (17.04)	6.8 (16.97)
Diarrhoea	5.8 (15.24)	5.8 (14.55)	5.8 (14.82)
Financial difficulties	19.8 (28.01)	19.4 (28.42)	19.6 (28.24)
QLQ-C30 summary score	84.9 (12.39)	84.8 (13.43)	84.8 (13.02)
EORTC QLQ-MY20 scores at study entry,[b,g] mean (SD)			
Disease symptoms	17.2 (16.08)	18.4 (17.51)	17.9 (16.96)
Side effects	13.3 (13.40)	12.5 (12.06)	12.8 (12.60)
Body image	79.7 (27.41)	80.8 (25.37)	80.4 (26.17)
Future perspective	68.7 (27.69)	69.9 (25.31)	69.4 (26.25)
Peripheral neuropathy	22.6 (27.99)	22.3 (28.45)	22.4 (28.25)

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20; IMiD, immunomodulatory drug; IQR, interquartile range; ISS, international staging system; MRD, minimal residual disease; PI, proteasome inhibitor; PR, partial response; sCR, stringent complete response; SD, standard deviation; VGPR, very good partial response.

[a]Age at date of informed consent is calculated as the integer part of (date of informed consent − date of birth)/365.25.

[b]Study entry is defined as the value collected at the time closest to, but prior to, the start of either study drug administration.

[c]Creatinine clearance was calculated for males as [140 − age (y)] × weight (kg)/[72 × serum creatinine (mg/dL)]. For females, that total was multiplied by 0.85.[37]

[d]High-risk cytogenetic abnormalities were detected by fluorescence in situ hybridisation or karyotype analysis and were defined as del(17p), t(4;14) and t(14;16). If all three abnormalities were unknown, indeterminate or missing, the patient was considered unclassifiable. There was no cut-off for defining the presence of del(17p).

[e]Time since initial diagnosis to the first dose of study treatment is calculated as (first dose date—date of initial diagnosis)/(365.25/12).

[f]Time since ASCT to first dose of treatment is calculated as (first dose date−date of ASCT)/(365.25/12).

[g]Higher scores for functional scales and QoL/summary score indicate higher functioning/QoL. Higher scores for symptoms and the Peripheral Neuropathy item indicate higher symptomatology.

number of assessment forms received divided by the total number of forms expected for each subject according to the protocol schedule.

For all analyses other than compliance, the analysis population comprised patients who reported HRQoL outcomes at study entry and completed at least one post–study entry assessment. Although the results for all subscale scores are presented in figures, this paper focuses on the subscales considered most clinically relevant in MM[18]: Global Health Status/QoL, Physical Functioning, Role Functioning, Pain, Nausea/Vomiting and Diarrhoea subscales of the EORTC QLQ-C30 and the Disease Symptoms subscale and Peripheral Neuropathy item of the EORTC QLQ-MY20. The time scale was defined in two ways: (a) in terms of 4-week intervals, including both time on treatment and the post-treatment phase (to capture the overall patient experience throughout the course of the trial), and (b) by treatment cycle (to capture patients' experiences specifically while on protocol treatment; see Appendix S1). Our main focus was on the overall patient experience. The value at study entry was defined as the value collected at the time closest to, but prior to, the start of study drug administration. Descriptive summaries of the mean (standard deviation [SD]) scores at study entry are shown in Table 1.

Change from study entry in EORTC QLQ-C30 and EORTC QLQ-MY20 subscale scores was analysed using a linear mixed-effects model. Linear mixed-effects models examine trends over time under the missing-at-random assumption. Separate groups of models were fit for each time scale. At each 4-week interval, least-squares mean change in score and least-squares mean difference between treatment arms were calculated with two-sided 95% confidence intervals (CIs). *P* values are descriptive and computed from the two-sided significance test at the alpha level of .05 for the coefficient of the interaction between treatment and visit and are reported without adjustment for multiple comparisons. Least-squares mean score differences between the ixazomib arm and the placebo arm, with two-sided 95% CIs, were examined over time, with particular focus on differences at interval 3 (to capture early toxicities likely to emerge with active treatment), interval 12 (halfway through planned treatment), interval 24 (representing the planned end of treatment) and interval 30 (representing the end of follow-up). For the cycle-based time scale, similar models were fit where cycle replaced 4-week interval in the models and only time on treatment was included.

A sensitivity analysis was conducted to examine the missing-at-random assumption of the interval-based, linear mixed-effects models, and the proportion of patients with stable scores or improved scores from study entry on the EORTC QLQ-C30 and QLQ-MY20 were calculated. Results from these analyses are shown in Appendix S1.

All analyses were conducted using SAS statistical software, version 9.2 or higher.

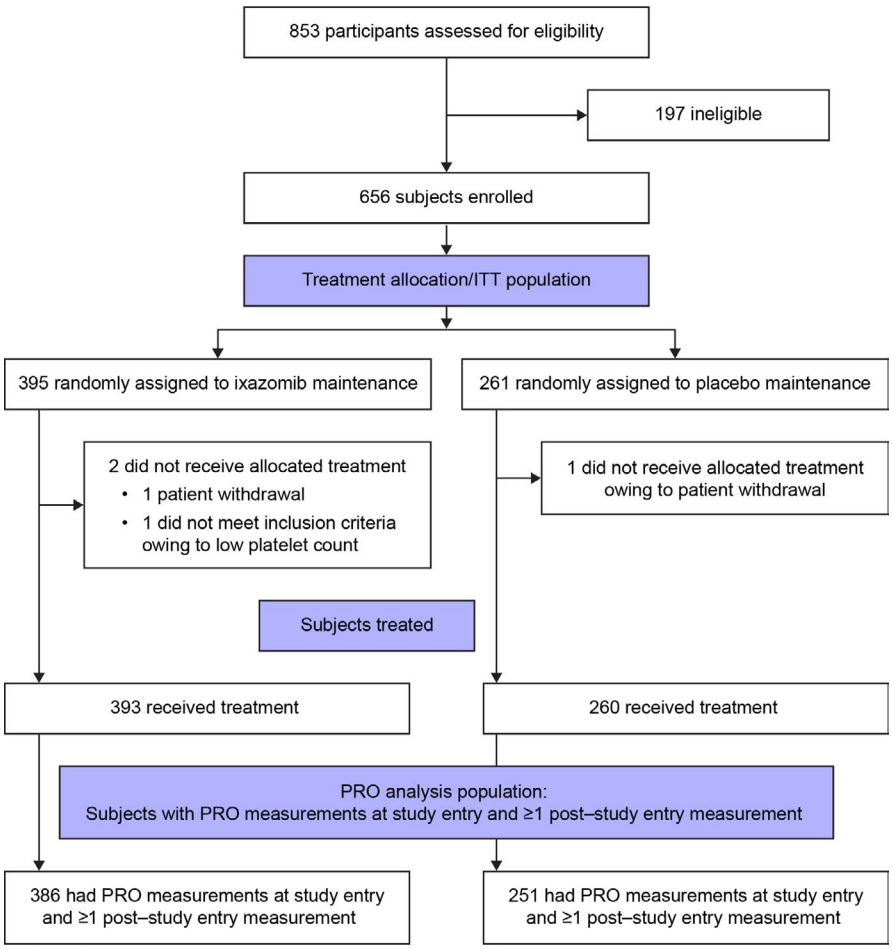

FIGURE 1 CONSORT diagram. ITT, intention to treat; PRO, patient-reported outcome [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Compliance with patient-reported outcome assessments

Visit	Placebo		Ixazomib	
	Expected, n	Received, n (%)	Expected, n	Received, n (%)
EORTC QLQ-C30				
Study entry	261	252 (97)	395	388 (98)
Cycle 2	259	250 (97)	390	376 (96)
Cycle 3	254	243 (96)	379	361 (95)
Cycle 4	252	242 (96)	376	364 (97)
Cycle 5	244	235 (96)	369	353 (96)
Cycle 6	233	223 (96)	360	349 (97)
Cycle 7	225	217 (96)	352	338 (96)
Cycle 8	218	208 (95)	344	331 (96)
Cycle 9	212	206 (97)	337	329 (98)
Cycle 10	206	198 (96)	329	319 (97)
Cycle 11	203	198 (98)	311	300 (96)
Cycle 12	202	196 (97)	305	295 (97)
Cycle 13	192	181 (94)	301	290 (96)
Cycle 14	189	184 (97)	294	286 (97)
Cycle 15	178	172 (97)	286	280 (98)
Cycle 16	171	166 (97)	276	266 (96)
Cycle 17	164	158 (96)	266	262 (98)
Cycle 18	157	151 (96)	256	250 (98)
Cycle 19	151	146 (97)	251	248 (99)
Cycle 20	144	140 (97)	248	248 (100)
Cycle 21	141	138 (98)	246	239 (97)
Cycle 22	135	128 (95)	238	235 (99)
Cycle 23	126	121 (96)	227	227 (100)
Cycle 24	122	117 (96)	221	218 (99)
Cycle 25	117	115 (98)	209	206 (99)
Cycle 26	111	109 (98)	190	185 (97)
All cycles before EOT	4867	4694 (96)	7756	7543 (97)
EOT	261	240 (92)	393	351 (89)
Total for post-EOT visits	1502	968 (64)	2299	1532 (67)
Overall total	6630	5902 (89)	10 448	9426 (90)
EORTC QLQ-MY20				
Study entry	261	252 (97)	395	388 (98)
Cycle 4	252	238 (94)	376	354 (94)
Cycle 7	225	210 (93)	352	330 (94)
Cycle 10	206	190 (92)	329	307 (93)
Cycle 13	192	178 (93)	301	285 (95)
Cycle 16	171	160 (94)	276	259 (94)
Cycle 19	151	144 (95)	251	240 (96)
Cycle 22	135	125 (93)	238	226 (95)
Cycle 25	117	114 (97)	209	202 (97)
All cycles before EOT	1710	1611 (94)	2727	2591 (95)

(Continues)

TABLE 1 (Continued)

Visit	Placebo		Ixazomib	
	Expected, n	Received, n (%)	Expected, n	Received, n (%)
EOT	261	235 (90)	393	344 (88)
Total for post-EOT visits	1502	958 (64)	2299	1523 (66)
Overall total	3473	2804 (81)	5419	4458 (82)

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20; EOT, end of treatment.

3 | RESULTS

3.1 | Characteristics at study entry

Of the 656 patients who were enrolled and randomly assigned to receive ixazomib MT or placebo in TOURMALINE-MM3, 637 (97%) reported HRQoL outcomes at study entry, completed at least one post–study entry assessment, and were included in the PRO analysis population (Figure 1). At study entry, demographic and disease characteristics were well balanced between the ixazomib (n = 386) and placebo (n = 251) arms of the PRO analysis population (Table 1). Across both arms, median age was 58 years (interquartile range, 52-64), 79% of patients had at least a very good partial response post-ASCT at study entry, 80% of patients were white, and 97% of patients had an ECOG performance status of 0 or 1. The characteristics were similar to those of the overall intent-to-treat population in TOURMALINE-MM3.[13]

At study entry, scores on the EORTC QLQ-C30 and EORTC QLQ-MY20 were high for functional scales and low for symptom scales and were similar between ixazomib and placebo arms. Moreover, EORTC QLQ-C30 subscale scores at study entry for both treatment arms were similar to scores for the general population (Table 1). On the EORTC QLQ-C30 subscales, mean (SD) scores for the ixazomib and placebo arms, respectively, were 71.0 (18.35) and 70.4 (16.67) for Global Health Status/QoL; 81.3 (18.62) and 81.3 (17.32) for Physical Functioning; 73.2 (28.56) and 73.2 (25.90) for Role Functioning; 23.4 (24.34) and 23.8 (24.84) for Pain; 3.2 (9.58) and 2.9 (10.52) for Nausea/Vomiting; and 5.8 (14.55) and 5.8 (15.24) for Diarrhoea. On the EORTC QLQ-MY20 subscales, mean (SD) scores for the ixazomib and placebo arms, respectively, were 18.4 (17.51) and 17.2 (16.08) for the EORTC QLQ-MY20 Disease Symptoms subscale and 22.3 (28.45) and 22.6 (27.99) for the Peripheral Neuropathy item.

3.2 | Compliance with HRQoL assessments

Compliance with HRQoL assessments was high at each cycle visit (≥90%) and was similar across treatment groups (Table 2). Compliance at all cycle visits prior to the end-of-treatment assessment and at the end-of-treatment assessment was 97% and 89% in the ixazomib arm, and 96% and 92% in the placebo arm for the EORTC QLQ-C30; 95% and 88%, and 94% and 90%, respectively, for the EORTC QLQ-MY20. Compliance with HRQoL assessments decreased after the end of treatment (across all post–end-of-treatment visits: EORTC QLQ-C30, 67% in the ixazomib arm and 64% in the placebo arm; EORTC QLQ-MY20: 66% and 64%, respectively).

3.3 | EORTC QLQ-C30 and EORTC QLQ-MY20 scores: Change with treatment

In the interval-based analysis, patients who discontinued treatment could continue to contribute to the analysis after stopping protocol therapy. In general, EORTC QLQ-C30 subscale scores remained relatively stable across the 4-week intervals in both treatment arms (Figure 2), and differences in the least square (LS) mean changes were generally similar between the ixazomib and placebo arms (Table 3). Even when differences between treatment groups were statistically significant ($P < .05$, without adjustment for multiple comparisons), the point estimates were small, and no differences reached the established MID of 10 (Figure 2).

On the EORTC QLQ-C30 Global Health Status/QoL subscale, both the ixazomib and placebo arms showed stable scores across the 30 intervals, with similar LS mean changes between arms (Figure 2A). Although LS mean changes showed little to no difference between arms at the clinically relevant time points (intervals 3, 12, 24 or 30; see Table 3), LS mean (95% CI) differences with *P* values <.05 did occur at interval 15 (3.0 [0.2-5.8]), interval 18 (3.4 [0.5-6.2]) and interval 21 (3.2 [0.3-6.2]). Similarly, across the 30 intervals, both treatment arms showed stable Physical Functioning subscale scores, with similar LS mean changes between arms (Figure 2B). LS mean (95% CI) differences between arms with *P* values <.05 were observed at interval 15 (2.4 [0.2-4.6]) and interval 21 (2.4 [0.1-4.8]) but not at intervals 3, 12, 24 or 30. Towards the planned end of treatment (at interval 24), there was a trend towards increasing scores on the Pain subscale in the ixazomib arm (Figure 2H): LS mean (95% CI) differences with *P* values <.05 occurred at interval 6 (−3.5 [−6.7, −0.4]), interval 21 (−5.1 [−8.7 to −1.5]) and interval 24 (−5.5 [−9.1 to −1.8]) but not at intervals 3, 12 or 30. Role Functioning scores were relatively stable and similar between treatment arms through the planned end of treatment at interval 24, increased in both arms at interval 27 and diverged at interval 30; LS mean (95% CI) differences with *P* values <.05 occurred only at interval 15 (4.2 [0.8, 7.6]) and interval 30 (6.7

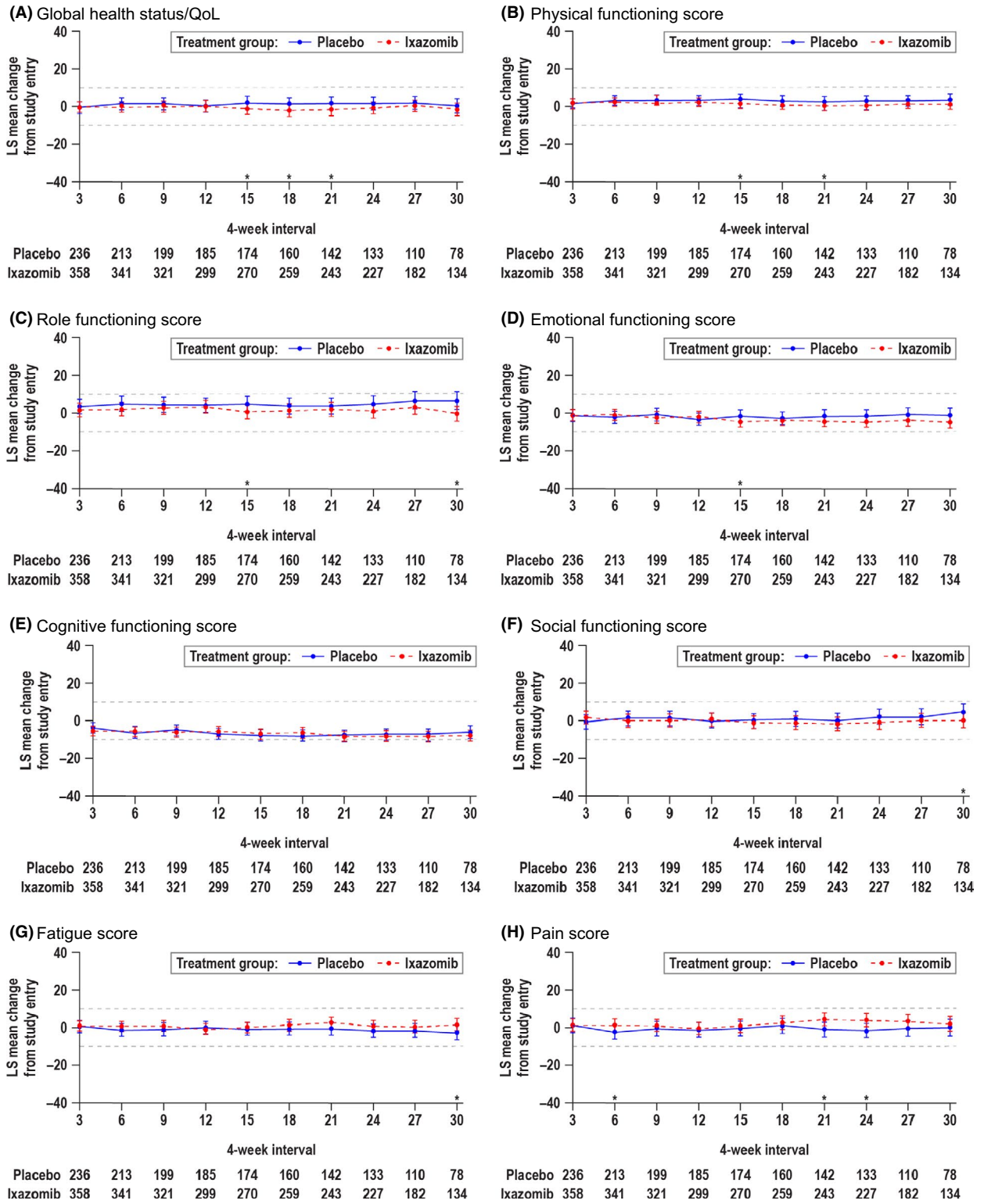

FIGURE 2 Linear mixed-effects model: Change from study entry in EORTC QLQ-C30 subscale scores and summary score across 4-week intervals. *P for difference ≤.05. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30. Note: Least-squares mean change from study entry in subscale scores is analysed using the repeated-measures linear mixed-effects models, including treatment group, visit, the interaction between treatment group and visit, study entry score, preinduction regimen (proteasome inhibitor vs immunomodulatory drug vs both proteasome inhibitor and immunomodulatory drug), international staging system (ISS) (stage I vs stage II or III), and response after transplantation (complete response or very good partial response vs partial response) at screening as covariates. Higher scores for functional scales and QoL/summary score indicate higher functioning/QoL. Higher scores for symptoms indicate higher symptomology [Colour figure can be viewed at wileyonlinelibrary.com]

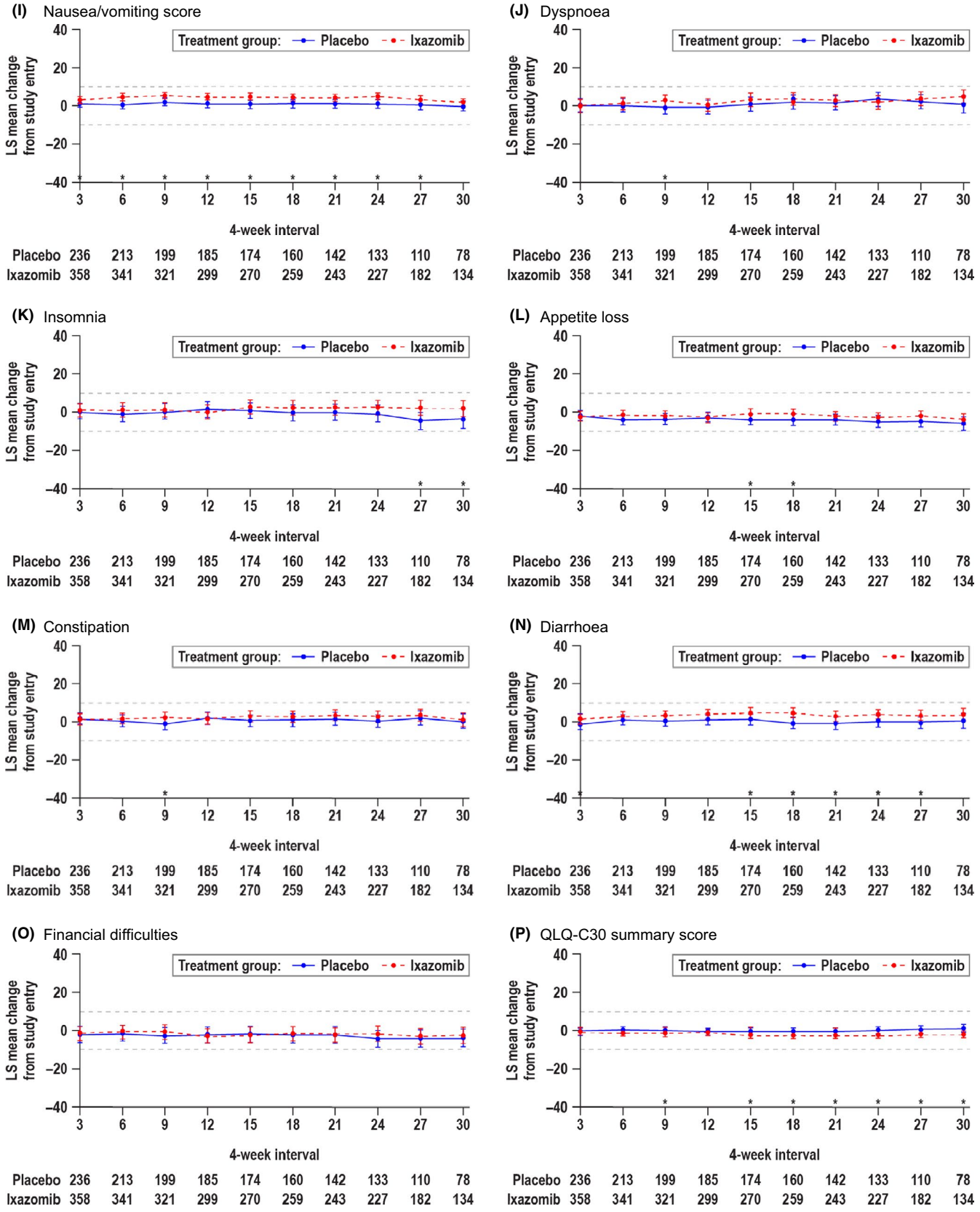

FIGURE 2 (Continued)

[2.3, 11.1]) (Figure 2C). Scores on the EORTC QLQ-C30 Nausea/Vomiting and Diarrhoea subscales, while consistently worse for ixazomib than placebo, were generally stable across the 30 intervals and were in line with the ixazomib toxicity profile. LS mean treatment differences with *P* values <.05 occurred at all intervals except interval 30 for the Nausea/Vomiting subscale (Figure 2I) and at intervals 3 and 15 through 27 for the Diarrhoea subscale (Figure 2N). No treatment differences reached the MID of 10 on any of the EORTC QLQ-C30 subscales.

Similarly, scores on most EORTC QLQ-MY20 subscales were relatively stable across 4-week intervals in both treatment arms. LS mean changes in EORTC QLQ-MY20 subscale scores also were generally similar between the treatment arms across the 30 intervals (Figure 3; Table 3). The ixazomib and placebo arms showed stable scores on the Disease Symptoms subscale across the 30 intervals (Figure 3B); an LS mean (95% CI) difference between treatment arms with *P* value <.05 occurred only at interval 24 (−4.4 [−7.3 to −1.4]) and not at intervals 3, 12 or 30. LS mean changes over time in Peripheral Neuropathy scores showed a trend towards improvement in the placebo arm and generally stable scores in the ixazomib arm (Figure 3E), with a significant LS mean (95% CI) difference with *P* value <.05 occurring only at interval 24 (−5.5 [−10.4 to −0.6]) (Table 3). No treatment differences between the ixazomib and placebo arms exceeded a threshold of 10 points for any EORTC QLQ-MY20 subscale.

Results of the additional analyses are shown in Appendix S1. Results of the alternative analysis of cycle-based changes from study entry in EORTC QLQ-C30 and EORTC QLQ-MY20 subscale scores were generally consistent with those from the interval-based analysis (Figures S1 and S2). Sensitivity analyses examining the missing-at-random assumption using a pattern-mixture model generally showed consistent results with the linear mixed-effects model results. Generally similar proportions of patients in the ixazomib and placebo arms had stable or improved scores, according to a 10-point threshold, on EORTC QLQ-C30 and QLQ-MY20 subscales (Figures S3 and S4).

4 | DISCUSSION

To date, TOURMALINE-MM3 has been the only double-blind, placebo-controlled, randomised controlled trial to evaluate MT post-ASCT, and the PRO results reported here are the first to be reported from such a trial. These analyses indicate that HRQoL was generally maintained during MT in both the ixazomib and placebo arms.

At study entry, EORTC QLQ-C30 scores were high for functioning and low for symptoms and were similar to those of the general population.[23] Most patients had experienced at least a very good partial response post-ASCT, and nearly all had an ECOG performance status of 0 or 1. Thus, the study population was largely asymptomatic and had a high level of functioning at study entry.

Prior research has shown that in the cancer setting in general, patients eligible for MT are often asymptomatic and seek to maintain HRQoL in addition to extending disease control.[24] Consistent with the aims of MT after ASCT—to prolong response while maintaining HRQoL—notable improvements in HRQoL and symptomatology were not expected in TOURMALINE-MM3; rather, the goal was to maintain the high level of functioning and minimal disease burden patients exhibited at study entry. EORTC QLQ-C30 and EORTC QLQ-MY20 subscale scores were relatively stable throughout the study, with comparable score changes between ixazomib and placebo groups. In particular, scores on the EORTC QLQ-C30 Global Health Status/QoL and Physical Functioning subscales were stable, with similar score changes between treatment arms. These results suggest that the high levels of HRQoL and functioning observed at study entry were maintained during treatment.

Scores on the EORTC QLQ-MY20 Disease Symptom subscale were relatively stable in the placebo arm. This finding is somewhat surprising: some worsening over time was expected, as placebo-treated patients had a shorter time to progression than ixazomib-treated patients.[13] Relatively stable Disease Symptom scores could be a function of placebo patients progressing biochemically, without symptoms or of average scores not detecting the relatively small proportion of patients progressing with symptoms.

The improvements in EORTC QLQ-MY20 Peripheral Neuropathy scores observed over time in the placebo arm were not unexpected: 90% of patients receiving placebo had received an induction regimen containing a proteasome inhibitor, a class for which peripheral neuropathy is a well-recognised toxicity. As any peripheral neuropathy events associated with placebo patients' induction regimen improved post-induction, improving scores on the EORTC QLQ-MY20 Peripheral Neuropathy item would have been expected. In comparison, stable EORTC QLQ-MY20 Peripheral Neuropathy scores, on average, among the ixazomib arm are likely an effect of improvement in peripheral neuropathy post-induction alongside potential treatment-emergent peripheral neuropathy events. While not directly comparable with patients' experiences of peripheral neuropathy collected via the EORTC QLQ-MY20, physician-reported AE rates from TOURMALINE-MM3 indicate that a minority of patients on ixazomib and placebo experienced peripheral neuropathy AEs (19% and 15%), all but 1 of which were grade 1 or 2.

A trend towards increasing EORTC QLQ-C30 Pain scores was observed towards the end of treatment in the ixazomib arm. This observation is difficult to explain from a clinical perspective but may be related to painful peripheral neuropathy. Nevertheless, differences between the ixazomib and placebo groups on the EORTC QLQ-C30 Peripheral Neuropathy item were minimal and not statistically significant. Further, as for all other EORTC QLQ-C30 and EORTC QLQ-MY20 subscales, no differences between treatment groups reached a threshold of 10.

The EORTC QLQ-C30 Nausea/Vomiting and Diarrhoea subscale scores were statistically significantly worse in the ixazomib arm than in the placebo arm, consistent with the known toxicity profile of ixazomib. While a 10-point threshold corresponding to a medium clinically meaningful effect was chosen to interpret the clinical meaningfulness of between-group differences in EORTC QLQ-C30 and QLQ-MY20 subscale score changes, statistically

TABLE 3 Treatment group differences in EORTC QLQ-C30 and QLQ-MY20 subscale scores across 4-week intervals, linear mixed-effects model

	4-wk interval EORTC subscale	Placebo vs ixazomib: LS mean difference (SE)	95% CI
EORTC QLQ-C30[a]			
Global health status/QoL	Interval 3	−0.5 (1.30)	(−3.0 to 2.1)
	Interval 12	0.0 (1.40)	(−2.8 to 2.7)
	Interval 24	2.1 (1.56)	(−0.9 to 5.2)
	Interval 30	1.8 (1.89)	(−1.9 to 5.5)
Physical functioning	Interval 3	−0.3 (1.03)	(−2.3 to 1.8)
	Interval 12	0.7 (1.10)	(−1.5 to 2.8)
	Interval 24	2.3 (1.21)	(0.0 to 4.7)
	Interval 30	2.4 (1.44)	(−0.5 to 5.2)
Role functioning	Interval 3	1.8 (1.59)	(−1.3 to 4.9)
	Interval 12	0.8 (1.70)	(−2.5 to 4.1)
	Interval 24	3.7 (1.88)	(0.0 to 7.4)
	Interval 30	6.7 (2.25)	(2.3 to 11.1)
Pain	Interval 3	−0.1 (1.56)	(−3.2 to 2.9)
	Interval 12	−0.9 (1.68)	(−4.2 to 2.4)
	Interval 24	−5.5 (1.87)	(−9.1 to −1.8)
	Interval 30	−1.8 (2.26)	(−6.2 to 2.7)
Nausea/Vomiting	Interval 3	−1.9 (0.93)	(−3.7 to 0.0)
	Interval 12	−3.7 (1.02)	(−5.6 to −1.7)
	Interval 24	−4.0 (1.16)	(−6.3 to −1.8)
	Interval 30	−1.7 (1.45)	(−4.6 to 1.1)
Diarrhoea	Interval 3	−2.8 (1.33)	(−5.4 to −0.2)
	Interval 12	−2.6 (1.46)	(−5.5 to 0.3)
	Interval 24	−3.5 (1.66)	(−6.7 to −0.2)
	Interval 30	−3.3 (2.08)	(−7.3 to 0.8)
EORTC QLQ-MY20[a]			
Disease symptoms	Interval 3	1.6 (1.10)	(−0.5 to 3.8)
	Interval 12	1.6 (1.27)	(−0.9 to 4.1)
	Interval 24	−4.4 (1.50)	(−7.3 to −1.4)
	Interval 30	−2.0 (1.61)	(−5.2 to 1.1)
Peripheral neuropathy	Interval 3	−0.4 (1.81)	(−3.9 to 3.2)
	Interval 12	−1.8 (2.11)	(−5.9 to 2.3)
	Interval 24	−5.5 (2.52)	(−10.4 to −0.6)
	Interval 30	−3.6 (2.72)	(−9.0 to 1.7)

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20; EOT, end of treatment; LS, least squares; SE, standard error.

[a]Higher scores for functional scales and QoL/summary score indicate higher functioning/QoL. Higher scores for symptoms and the Peripheral Neuropathy item indicate higher symptomatology.

significant differences in some subscale scores noted between the arms nevertheless could be interpreted as small clinically meaningful effects.[16] For example, the symptom of nausea and vomiting was statistically significantly less burdensome among patients in the placebo arm compared with the ixazomib arm, with mean differences ranging from −3.0 to −4.1 at 4-week intervals 6 through 24, corresponding to small clinically meaningful differences.[16] Similarly, the symptom of diarrhoea was significantly worse in the ixazomib arm compared with the placebo arm at 4-week intervals 15 through 27; mean differences ranging from −3.5 to −5.5 during these intervals corresponded to small clinically meaningful differences.[16] The clinical relevance of the magnitude of these treatment differences is uncertain, but the patient-reported scores aligned with the side effect profile of predominantly low-grade

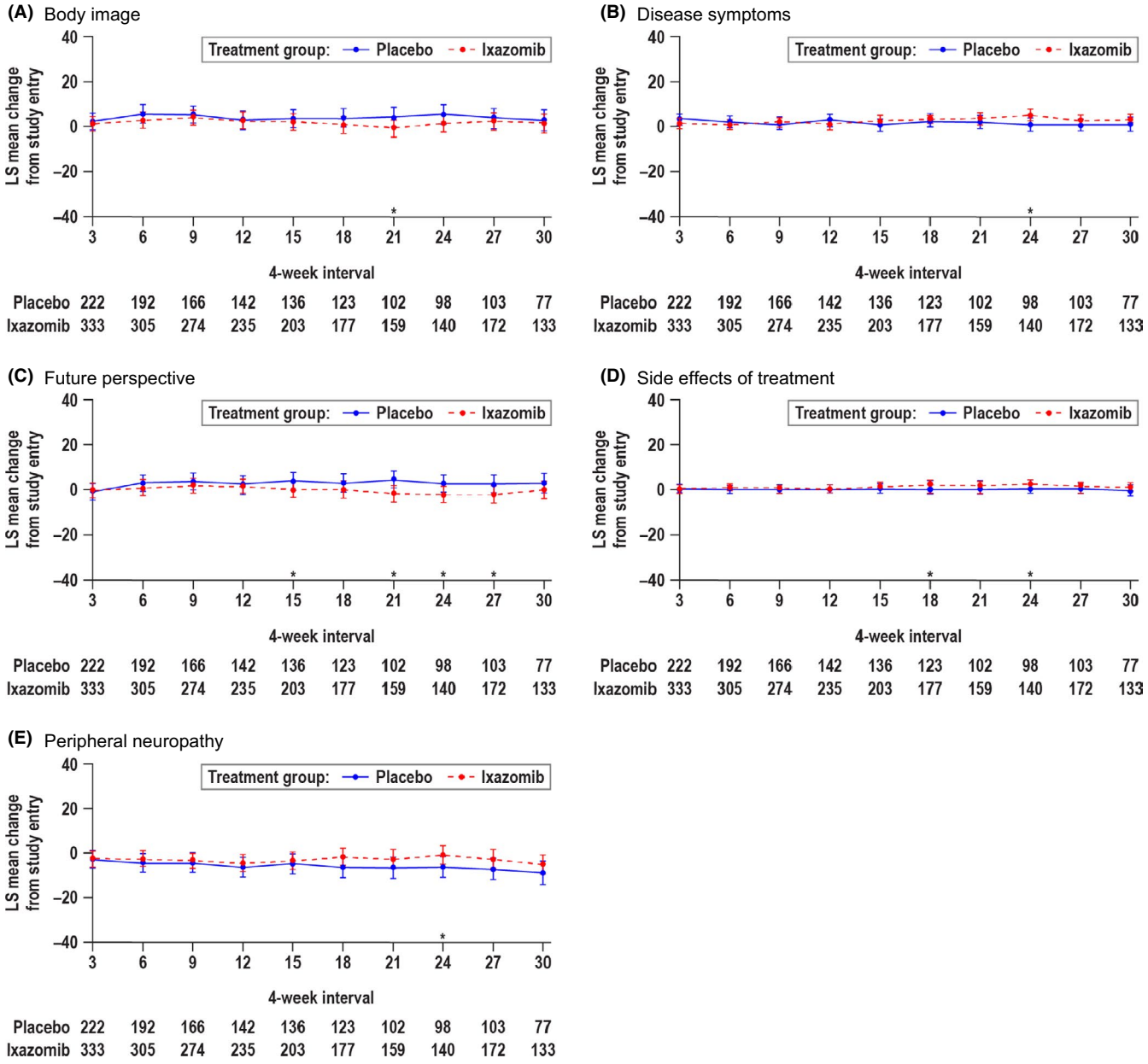

FIGURE 3 Linear mixed-effects model: Change from study entry in EORTC QLQ-MY20 subscale scores across 4-week intervals. **P* for difference ≤.05. EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20. Note: Least-squares mean change from study entry in subscale scores is analysed using the repeated-measures linear mixed-effects models, including treatment group, visit, the interaction between treatment group and visit, study entry score, pre-induction regimen (proteasome inhibitor vs immunomodulatory drug vs both proteasome inhibitor and immunomodulatory drug), international staging system (ISS) (stage I vs stage II or III), and response after transplantation (complete response or very good partial response vs partial response) at screening as covariates. Higher scores for functional scales and QoL/summary score indicate higher functioning/QoL. Higher scores for symptoms indicate higher symptomology. [Colour figure can be viewed at wileyonlinelibrary.com]

gastrointestinal events with ixazomib in TOURMALINE-MM3, in which 19% of patients received antiemetics.[13] Treatment decisions around ixazomib maintenance therapy should consider the trade-off of these low-grade side effects and their small clinically relevant impact as reported by patients for a prolongation of median PFS of 5.2 months compared with placebo.[13]

During treatment, compliance with HRQoL assessments by cycle was ≥90% and was similar across treatment groups. A sensitivity analysis using pattern-mixture modelling suggests that the main model was robust to deviations of the missing-at-random assumption. In addition, analyses of patients with stable or improved HRQoL over time revealed within-person changes to be similar to longitudinal treatment averages.

HRQoL and symptomatology, as subjective concepts, may be influenced not only by patients' evolving health condition or changes with treatment, but also by their psychological adaptation to their illness, a concept known as *response shift*.[14] MID estimates in MM have been shown to be generally robust to patients' adaptation to

their illness,[14] suggesting that the results of this analysis are not the effect of adaptive response during MT.

Prior studies, while limited, generally support our findings that HRQoL is maintained during MT for MM.[25-27] A double-blind randomised study evaluated an induction regimen followed by MT with lenalidomide or no MT in patients aged ≥65 years newly diagnosed MM who did not undergo an ASCT and found stable scores during MT on most EORTC QLQ-C30 subscales (including Physical Functioning, Fatigue and Pain) and EORTC QLQ-MY20 subscales; only EORTC QLQ-C30 Global Health Status/QoL scores showed statistically significant worsening during MT (mean change = −4.1, $P < .05$).[25] An observational registry study evaluating HRQoL during MT in patients with MM post-ASCT found no significant differences in EQ-5D index, Functional Assessment of Cancer Therapy—Multiple Myeloma (FACT-MM) total or Brief Pain Inventory scores between patients receiving MT with lenalidomide and those not receiving MT.[26] Finally, a nonblinded trial of patients with MM post-ASCT undergoing MT with thalidomide-prednisone maintenance or observation only reported a general worsening of HRQoL as evaluated by the EORTC QLQ-C30 and a trial-specific MM symptom module among patients receiving MT.[10] Specifically, patients receiving thalidomide-prednisone MT tended to report lower HRQoL scores for many symptoms and on the Global Health Status/QoL, Role Functioning and Cognitive Functioning domains.[10] Some limitations of these studies must be acknowledged, including limited descriptions of methods underlying the HRQoL analyses[26]; no assessment of treatment effect on overall HRQoL[25]; and open-label study designs,[10,26] which may introduce bias in PRO.[28,29] Studies evaluating MT across a variety of cancer settings also revealed that HRQoL tends to be similar between treatment arms during MT.[24,30-32]

The results of this analysis must be interpreted in view of several strengths and limitations. A key strength is this study's double-blinded design. Nevertheless, some analytic limitations must be noted. Peripheral neuropathy was evaluated in a post hoc analysis using a single EORTC QLQ-MY20 item focusing on symptoms of tingling in hands and feet alone. This single item may not fully capture patients' experiences of peripheral neuropathy. More broadly, the PRO measures employed in this analysis represent a subset of concepts that are important to patients with MM.[33] Future analyses should explore how MT affects other dimensions of HRQoL that may be important to patients (eg impacts of MM symptoms, health service factors).[33] Further, the ASCT-eligible TOURMALINE-MM3 population was relatively young and had few comorbidities, with high levels of physical functioning; as such, the study results are subject to potential selection bias. Nevertheless, the characteristics of populations from observational studies conducted among transplant-eligible patients with newly diagnosed MM provide some context for the representativeness of the TOURMALINE-MM3 population. Specifically, a National Cancer Database US population-based study of 12 378 patients with newly diagnosed MM who underwent frontline transplantation reported that 87% had no comorbidities according to the Charlson Comorbidity Index and 11% of patients had a Charlson Comorbidity score of 1.[34] Another observational study of 244 patients with newly diagnosed MM who underwent post-frontline transplantation maintenance therapy reported that, among patients with known ECOG performance status, 88% had an ECOG score of 0-1 prior to initiation of maintenance therapy.[35] It is acknowledged that the characteristics of the TOURMALINE-MM3 population may limit the generalisability of the findings to a wider real-world population—a known limitation of randomised controlled trials in MM more generally.[36]

A primary goal of MT in newly diagnosed MM post-ASCT is to prolong PFS. In TOURMALINE-MM3, ixazomib significantly prolonged PFS compared with placebo. At study entry, patients showed a high level of functioning, and HRQoL was maintained during MT in both ixazomib and placebo arms, with minimal and clinically insignificant impact of treatment. Active treatment with ixazomib did not have an adverse impact on HRQoL. As a uniquely suited option that fulfils the goals of MT—prolonging PFS, exhibiting no adverse impact on HRQoL and offering a favourable toxicity profile and convenient oral administration—ixazomib should be considered for MT in post-ASCT in individuals with newly diagnosed MM.

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CONFLICT OF INTEREST

This study was conducted under a research contract between Takeda Pharmaceuticals and RTI Health Solutions and was funded by Takeda Pharmaceuticals. LC, DR and KS are salaried employees of Takeda Pharmaceuticals. DO and AG are salaried employees of RTI Health Solutions. FS has participated in speaker bureaus for Amgen, Celgene, Takeda, AbbVie, and Janssen and is a member of advisory boards for Amgen, Celgene, Takeda, Janssen, Bristol-Myers Squibb, Bayer, Adaptive and Oncopeptides. HG has participated in advisory boards for Adaptive Biotechnology, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Sanofi and Takeda; has received research funding from Amgen, Bristol-Myers Squibb, Celgene, Chugai, Janssen, Sanofi, Mundipharma, Takeda and Novartis; and has received honoraria from ArtTempi, Bristol-Myers Squibb, Celgene, Chugai, Janssen and Novartis. VM has received personal fees from Takeda, Janssen, Amgen, Celgene, GlaxoSmithKline and AbbVie. AS provides consultancy for Specialised Therapeutics Australia; has received honoraria from Takeda, Celgene, Janssen and Amgen; has participated in

speaker bureaus for Takeda, Celgene and Janssen; and has received research funding from Takeda, Celgene, Janssen and GlaxoSmithKline. NA has received research grants from Celgene, Takeda, Janssen and Amgen, and has participated in scientific advisory board for Celgene, Takeda, Janssen, Amgen and Novartis. VR declares no competing interests; their employer, the Mayo Clinic, received research funding for the TOURMALINE-MM3 clinical trial. MAD is a consultant for Amgen, Celgene, Takeda, Janssen and Bristol-Myers Squibb; has received honoraria from Amgen, Celgene, Takeda and Janssen; and has participated in speaker bureaus for Amgen, Celgene, Takeda and Janssen.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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