Efficacy, safety, and health-related quality of life in transplant-ineligible newly diagnosed multiple myeloma patients receiving bortezomib maintenance therapy: a study of the Korean Multiple Myeloma Working Party KMMWP-174 study

Multiple myeloma (MM) remains incurable with inevitable relapse, requiring effective long-term treatment strategies for transplant-ineligible patients who make up a significant proportion of MM patients due to advanced age and comorbidities.[1,2] Maintenance therapy (MT) has emerged as a cornerstone strategy to sustain treatment responses, delay progression, and improve survival outcomes.[3-5] While lenalidomide maintenance is well-established, evidence supporting bortezomib MT in transplant-ineligible patients remains limited. This prospective multicenter single-arm observational study evaluated the impact of bortezomib MT on clinical efficacy, safety, and health-related quality of life (HRQoL) in real-world transplant-ineligible newly diagnosed MM (NDMM) patients, demonstrating effective disease control with an acceptable safety profile and manageable HRQoL outcomes.

This study was conducted across 14 institutions affiliated with the Korean Multiple Myeloma Working Party (KMMWP) between May 2017 and December 2021. Seventy-eight transplant-ineligible patients with NDMM who achieved partial response (PR) or better after induction chemotherapy were enrolled. The transplant-ineligible group refers to patients who, due to older age, high comorbid burden, or poor performance status, are at increased risk of treatment-related toxicities.[6] Ethics committees or institutional review boards at all study sites approved the study, which was carried out in accordance with the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice. All patients provided written informed consent.

The primary endpoint was progression-free survival (PFS), with secondary endpoints including secondary PFS (PFS2), overall survival (OS), toxicity, and HRQoL. Events of PFS were defined as progression or death. PFS2 was defined as the duration from the start of first-line treatment to the second relapse, progression, or death. OS was defined as the time from initiation of induction chemotherapy to death from any cause. Bortezomib MT was administered subcutaneously at 1.3 mg/m² once weekly for three weeks (days 1, 8, 15) at 28-day intervals[7] until disease progression or unacceptable toxicity. Patients without disease progression or significant adverse events (AE) received MT for up to 24 months before discontinuation. Dose reductions were applied based on toxicity severity. HRQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)[8] and its MM-specific module (QLQ-MY20)[9] validated tools at baseline (cycle 1, day 1 of MT) and on day 1 of each subsequent cycle throughout maintenance. A 10-point change or higher was considered clinically significant. All multi-item scales were scored according to the EORTC scoring manual. Statistical analyses included Kaplan-Meier survival estimates and paired *t* tests for HRQoL changes, with $P<0.05$ considered statistically significant.

The median age was 71.0 years (range: 56-83), with 23.1% aged ≥75 years. IgG MM was most prevalent (52.6%), followed by IgA (25.6%) and light chain (17.9%) MM. Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (98.7%) and International Staging System (ISS) stage II-III (71.8%). High-risk cytogenetics were present in 25.6% of patients. Moderate to severe renal impairment (glomerular filtration rate [GFR] <60 mL / minute [min] / 1.73 m²) occurred in 35.9% (Table 1). The majority (93.6%) received bortezomib + melphalan + prednisone (VMP) induction therapy. Median bortezomib MT cycles was 9.5 (range: 1-26) with a median duration of 9.4 months (*Online Supplementary Table S1*). With median follow-up of 44.5 months, median PFS was 27.2 months (95% Confidence Interval [CI]: 20.8-32.7), median PFS2 was 49.2 months (95% CI: 37.8-NA), and median OS was not reached (mean 83.7 months) (Figure 1). Subgroup analyses revealed notable variations across patient characteristics. Among ISS categories, the ISS-2 group showed 2-year PFS of 56.7 months and PFS2 of 88.0 months, whereas the ISS-3 group showed extended PFS2 of 85.7 months and OS of 96.3 months. Interestingly, there was no statistically significant difference in PFS (55.0 *vs*. 50.0 months), PFS2 (84.4 *vs*. 78.3 months), or OS (95.0 *vs*. 88.9 months) between the high-risk and standard-risk cytogenetic groups. Although these results suggest feasibility of bortezomib MT in high-risk patients, they should be interpreted with caution due to potential selection bias rather than reflecting true prognostic advantage. Severe renal impairment (estimated GFR <30 mL/min/1.73 m²) was associated with the lowest 2-year OS (88.9 months), indicating a need to

optimize management of this subgroup (*Online Supplementary Figure S1*).

Of 78 enrolled patients, 73 (93.6%) completed baseline and end-of-treatment (EOT) QoL assessments. EOT questionnaires were unavailable for 5 patients: 3 discontinued due to disease progression or AE, one died after cycle 24, and one completed cycle 26 but did not return the EOT questionnaire for unknown reasons. EORTC-QLQ-C30 analysis revealed a significant decline in global health status (GHS) / QoL from baseline (mean [SD] 61.32 [18.94]) to EOT (56.05 [20.85]; *P*=0.040). Multiple functional domains showed significant deterioration: role (*P*=0.045), and emotional (*P*=0.005), cognitive (P<0.001), and social (*P*=0.037) functioning. Among symptom measures, financial difficulties demonstrated the most notable increase from baseline (19.23 [24.33]) to EOT (28.24 [28.34]; *P*=0.009). The myeloma-specific QLQ-MY20 showed that disease symptoms and side effects increased marginally but not significantly. However, future perspective (FP) scores decreased significantly from baseline (69.94 [22.73]) to EOT (63.17 [26.64]; *P*=0.030), while body image (BI) scores showed a declining trend (*P*=0.080) (*Online Supplementary Table S2*). Longitudinal analysis demonstrated progressive decline in HRQoL compared to baseline, with EORTC-QLQ-C30 scores remaining within the predefined ± 10-point clinically meaningful threshold. EORTC-QLQ-MY20 scores showed more pronounced deterioration, particularly in FP and BI domains, occasionally exceeding the ± 10-point threshold, indicating clinically meaningful deterioration (Figure 2). Recent pooled analyses by Musoro *et al*. have provided updated minimally important differences (MID) for EORTC-QLQ-C30, indicating that domain-specific thresholds (typically 5-10 points) are required for appropriate interpretation.[10] Application of these contemporary standards suggests that observed changes in GHS and FP may represent small but clinically relevant deteriorations.

Bortezomib MT was well-tolerated, with 60.2% experiencing any AE and only 16.7% developing grade 3-4 events. Treatment discontinuation due to toxicity occurred in 3.8% with no treatment-related deaths. Most common any grade AE were fatigue (6.4%), diarrhea (7.7%), nausea/vomiting (6.4%), peripheral neuropathy (PN) (7.7%), and urticaria/pruritus (6.4%). Diarrhea (5.1%) was the most frequent grade 3-4 event. Hematologic toxicity was minimal with one case of grade 3-4 anemia (1.3%). Infectious complications were rare with one case of grade 3-4 pneumonia (1.3%). Notably, no PN cases led to treatment discontinuation. Secondary primary malignancy (SPM) occurred in one patient (1.3%) with breast cancer. The low incidence of PN and fatigue may be attributed to several factors. First, study inclusion criteria required PN grade ≤1 and ECOG ≤2 following induction, potentially introducing selection bias toward patients with better tolerance. Second, subcutaneous once-weekly administration for three consecutive weeks followed by a 1-week rest is associated with reduced severe PN compared to biweekly intravenous administration, as demonstrated in the HOVON-65/GMMG-HD4 trial.[11] Finally, under-reporting of subjective symptoms may have contributed to the low incidence rates observed.

Previous studies established lenalidomide maintenance in both transplant-eligible and -ineligible populations.[12-14] However, evidence supporting bortezomib MT, particularly in transplant-ineligible patients, remains limited. Our

Table 1. Clinical characteristics of patients.

Variables	Total N=78
Age, years, median (range)	71.0 (56-83)
<70 years, N (%)	25 (32.1)
70 to <75 years, N (%)	35 (44.8)
≥75 years, N (%)	18 (23.1)
Gender, N (%)	
Male	49 (62.8)
Female	29 (37.2)
Type of myeloma, N (%)	
IgG	41 (52.6)
IgA	20 (25.6)
IgM	0 (0)
IgD	1 (1.3)
IgE	1 (1.3)
Non-secretory	1 (1.3)
Light chain disease	14 (17.9)
Light chain type, N (%)	
Kappa	41 (52.6)
Lambda	37 (47.4)
ECOG performance status, N (%)	
0	50 (64.1)
1	27 (34.6)
2	1 (1.3)
ISS status at diagnosis, N (%)	
I	20 (25.6)
II	26 (33.3)
III	30 (38.5)
Unknown	2 (2.6)
Cytogenetic profile at diagnosis, N (%)	
Standard risk	20 (25.6)
High risk	20 (25.6)
Unknown	38 (48.7)
Blood values at baseline, median (range)	
β2-microglobulin, mg/mL	4.03 (0.23-25.04)
Albumin, g/dL	3.6 (2.1-4.9)
LDH >Upper limit of normal, N (%)	46 (59.0)
Hemoglobin, g/dL	11.3 (8.6-14.9)
Absolute neutrophil counts, x10^9/L	2.83 (1.16-7.52)
Absolute lymphocyte counts, x10^9/L	0.92 (0.22-4.20)
Platelet counts, x10^9/L	171 (82-335)
GFR, mL/min/1.73 m^2, median (range)	69 (5-125)
≥ 60 mL/min/1.73 m^2, N (%)	50 (64.1)
30 to < 60 mL/min/1.73 m^2, N (%)	18 (23.1)
< 30 mL/min/1.73 m^2, N (%)	10 (12.8)

ECOG: Eastern Cooperative Oncology Group; GFR: glomerular filtration rate; ISS: International Staging System; LDH: lactate dehydrogenase; min: minute; N: number.

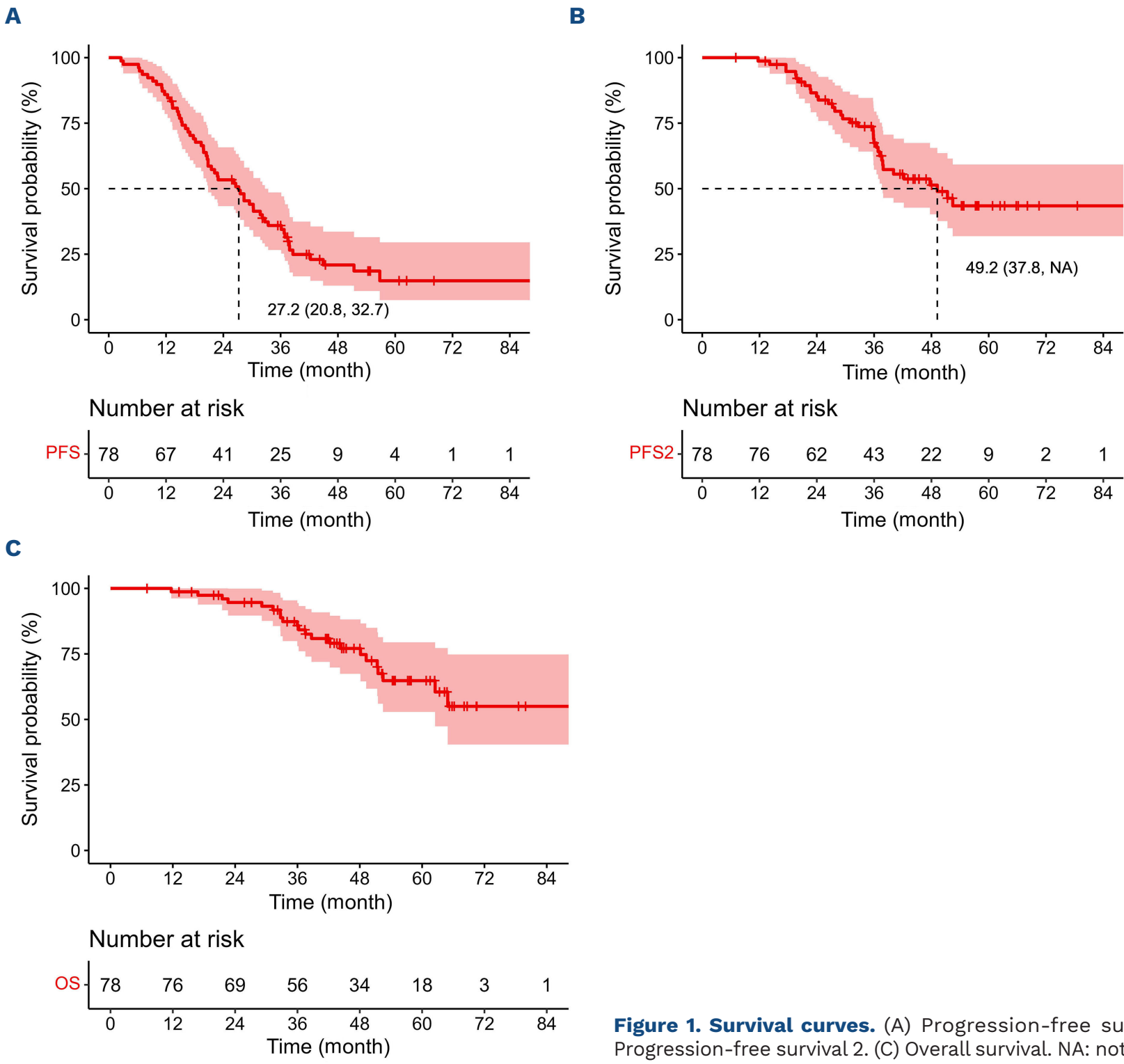

Figure 1. Survival curves. (A) Progression-free survival. (B) Progression-free survival 2. (C) Overall survival. NA: not achieved.

results demonstrate that bortezomib MT substantially prolongs disease control with a manageable safety profile. The median PFS of 27.2 months was consistent with previous clinical trials, including the GEM2005MAS65,[5] which demonstrated significant survival benefits with bortezomib-based maintenance. Although no prior studies had directly compared toxicity profiles of bortezomib and lenalidomide maintenance, our results support bortezomib MT as a viable long-term option with acceptable safety profile. Financial distress significantly increased over time, consistent with previous reports that long-term MT leads to substantial financial burden due to extended treatment duration.[15] The progressive decline in FP scores (Figure 2) reflects patient concerns about the long-term uncertainty of the disease trajectory and treatment, particularly relevant given the incurable nature of MM, despite improved survival outcomes. The generic formulation of bortezomib used in this study may offer a cost-effective approach for sustaining long-term MT.

Several limitations should be considered. Firstly, this single-arm study limits any clear interpretation of efficacy and HRQoL outcomes. The absence of comparators such as lenalidomide or observation undermines the strength of our conclusions. Secondly, although this was a multicenter study, the relatively small sample size (N=78) may limit generalizability. The inclusion of a single patient (1.3%) with ECOG performance status 2 could have influenced the external validity of the results. Moreover, enrolling only patients who achieved at least PR to induction therapy may introduce selection bias. However, as MT is conventionally administered to patients with an adequate response to initial treatment, this criterion is consistent with standard clinical practice and aligns with the study objectives. Thirdly, subgroup analyses in high-risk cytogenetic subgroups

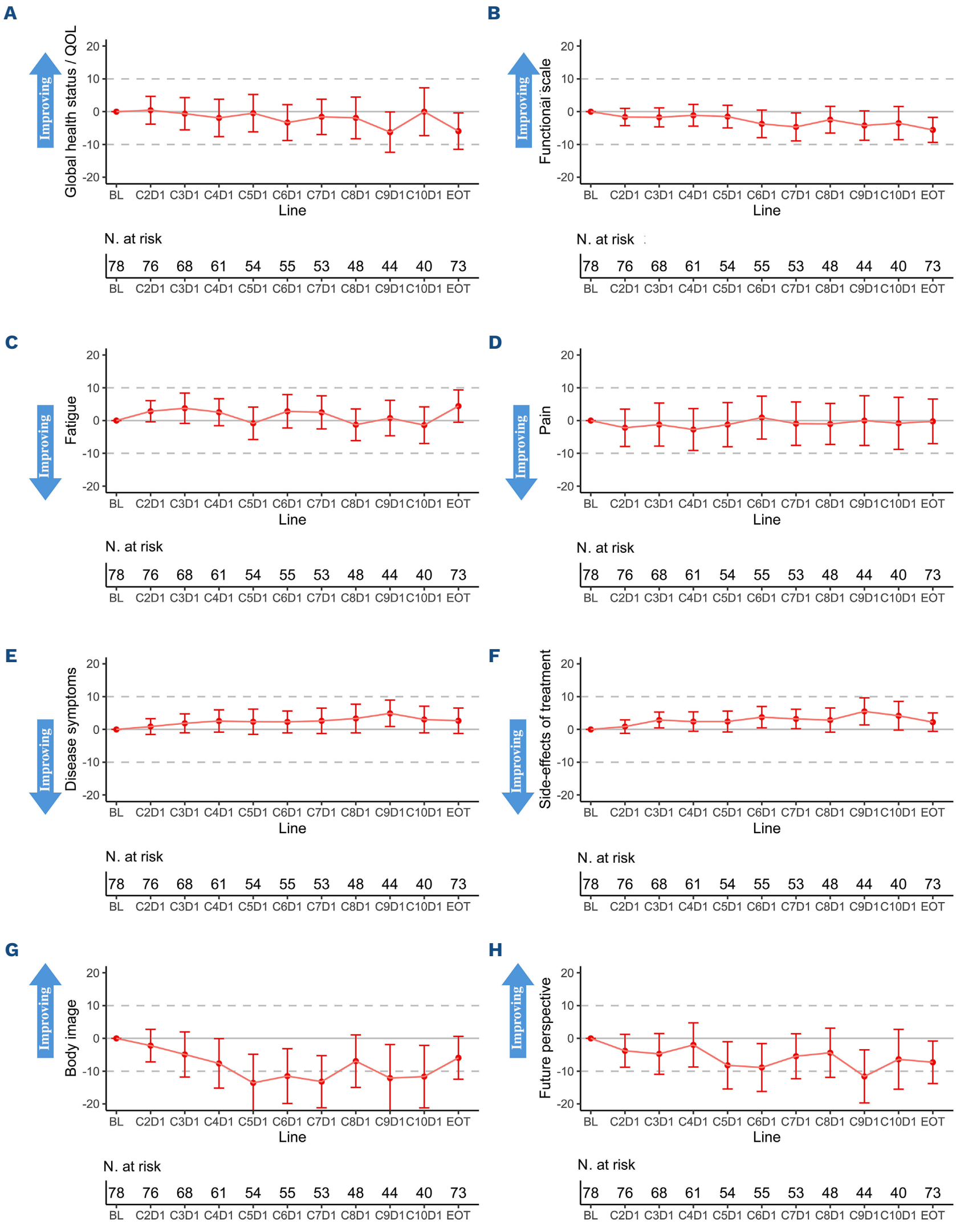

Figure 2. Mean observed scores for the EORTC-QLQ-C30 and EORTC-QLQ-MY20 domains in line of treatment. (A) Global health status / Quality of Life (QoL). (B) Functional scale. (C) Fatigue. (D) Pain. (E) Disease symptoms. (F) Side-effects of treatment. (G) Body image. (H) Future perspective. N: number.

were based on limited numbers and need to be interpreted with caution. Furthermore, HRQoL participation decreased significantly after cycle 10 (to <50%), potentially biasing outcomes for later treatment phases. Finally, the median follow-up of 44.5 months was insufficient for long-term OS assessment as the median OS was not reached.

In conclusion, bortezomib MT provides effective disease control with an acceptable safety profile in transplant-ineligible MM patients. Despite some decline in HRQoL over time, changes remained within clinically tolerable thresholds, supporting bortezomib as a viable maintenance option. These real-world findings complement existing clinical trial data and support the use of bortezomib MT in clinical practice for transplant-ineligible MM patients. Further studies with larger sample sizes, longer follow-up, and comprehensive HRQoL assessments are warranted to optimize maintenance strategies and improve patient outcomes.

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Disclosures

JYL, S-SP, JSK, J-JL, SKP, HJK, G-WL, YHP, H-SE, J-AK, MKK, YK, H-JS, HSL, JK and C-KM report consultancy and research funding from ACE pharma Korea. All of the other authors have no conflicts of interest to disclose.

Contributions

C-KM conceptualized and designed the research. SJ and SC performed statistical analysis and wrote the section on the statistical analysis. JYL, S-SP, JSK, J-JL, SKP, HJK, G-WL, YHP, H-SE, J-AK, MKK, YK, H-JS, HSL, JK and C-KM collected and managed the patients' database. Patient information was provided by various investigators from the KMMWP. All authors contributed to the preparation of the manuscript and approved the final version for publication.

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Data-sharing statement

The data that support the findings of this study are not publicly available due to privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

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