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RESEARCH

Real-world effectiveness of bortezomib maintenance following VMP induction in transplant-ineligible multiple myeloma: a target trial emulation study

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Abstract

Bortezomib-melphalan-prednisone (VMP) is an established induction regimen for transplant-ineligible newly diagnosed multiple myeloma (NDMM), yet optimal post-induction strategies remain unclear. This study evaluated the effectiveness of bortezomib maintenance following VMP using target trial emulation. We compared a prospective maintenance cohort (KMMWP-174 study) with an external control cohort from a multicenter registry. Eligible patients completed 9 VMP cycles, achieved≥partial response, and were progression-free for 60 days. The index date was maintenance initiation for cases and day 60 post-VMP for controls. Propensity score matching (1:1) balanced baseline covariates. The primary endpoint was progression-free survival (PFS); overall survival (OS) was secondary. Sensitivity analyses included multivariable regression, landmark analyses, and E-value assessment. Among 178 eligible patients, 60 comprised the maintenance cohort and 118 the control cohort; 54 per group were analyzed after matching. Median PFS was significantly longer with bortezomib maintenance (26.5 vs. 8.8 months; HR 0.437, 95% CI: 0.275–0.694, P<0.001). PFS benefits were consistent across subgroups, including patients aged≥70 years, those with ISS stage II-III disease, and those with high-risk cytogenetics. OS showed a favorable trend (HR 0.703, P=0.252). Grade≥3 adverse events occurred in 31.4% (control) and 18.7% (maintenance). No grade≥3 peripheral neuropathy was observed. Bortezomib maintenance following VMP significantly prolonged PFS in transplant-ineligible NDMM with acceptable toxicity. These real-world data support proteasome inhibitor-based maintenance where VMP remains widely used, particularly among older adults with limited treatment options.

Keywords Multiple myeloma · Bortezomib · Maintenance chemotherapy · Proteasome inhibitors · Comparative effectiveness research · Target trial emulation

Introduction

Multiple myeloma (MM) is a clonal plasma cell malignancy accounting for approximately 1% of all cancers and 10% of hematologic malignancies worldwide [1, 2]. The median age at diagnosis is around 70 years, and a substantial proportion of patients are ineligible for autologous stem cell transplantation (ASCT) due to frailty, comorbidities, or organ dysfunction [1–3]. Despite therapeutic advances incorporating proteasome inhibitors (PIs), immunomodulatory drugs, and monoclonal antibodies, MM remains incurable, and relapse is inevitable for most patients [3–7]. Therefore, effective and well-tolerated long-term treatment strategies are essential for transplant-ineligible newly diagnosed MM (NDMM) patients.

For transplant-ineligible patients, bortezomib-melphalan-prednisone (VMP) is established as standard induction

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regimen based on the landmark VISTA trial, which demonstrated superior progression-free survival (PFS) and overall survival (OS) compared to melphalan-prednisone alone [8]. This trial showed that VMP significantly enhanced median time to progression (24.0 vs. 16.6 months; HR: 0.48, $P < 0.001$) and OS (56.4 vs. 43.1 months; HR: 0.65, $P < 0.001$) in NDMM patients ineligible for transplantation. However, despite these improvements, the optimal post-induction strategy following VMP remains to be determined.

Maintenance therapy (MT) has emerged as a cornerstone of MM management in transplant-eligible patients, with objectives of sustaining treatment responses, delaying disease progression, and ultimately improving PFS and OS [3–6]. However, the role of MT is less well-defined for transplant-ineligible patients lacking the benefit of high dose chemotherapy and ASCT. Nonetheless, unlike traditional intermittent treatments, MT provides continuous therapeutic pressure against residual disease, and thereby minimizes relapse risk and extends survival in this vulnerable population [8–12].

Among available MT agents, bortezomib, a first-in-class PI, has demonstrated significant efficacy in transplant-eligible and -ineligible patients with MM [3]. Clinical trials, such as the GEM2005MAS65 trial, have established the benefit of bortezomib-based maintenance regimens, demonstrating significant extensions in PFS and OS, particularly in high-risk cytogenetic subgroups [5]. Our previous study demonstrated the efficacy of bortezomib MT in transplant-ineligible MM patients, with median PFS of 27.2 months, median PFS2 of 49.2 months, and an unreached median OS [13]. However, real-world evidence regarding bortezomib maintenance following standard VMP induction in transplant-ineligible patients remains limited [14].

While bortezomib MT has demonstrated survival benefits, toxicity management remains a significant challenge. Peripheral neuropathy (PN), fatigue, and gastrointestinal (GI) symptoms are notable adverse events (AEs) that affect long-term compliance and quality-of-life (QoL) [3–6]. Subcutaneous administration has significantly reduced injection-related AEs, maintained efficacy, and improved feasibility of long-term treatment [14].

Despite the availability of contemporary regimens, VMP continues to be utilized in many healthcare systems, particularly in Asia, Eastern Europe, and Latin America, where access to newer agents is constrained by cost, reimbursement policies, or regulatory factors [15]. In Korea, VMP remained a standard option during our study period (2010–2021) and continues to be prescribed for selected patients, including those with renal impairment, thrombotic risk, or advanced age with comorbidities. Given the increasing prevalence of MM in the elderly population and the challenges facing transplant-ineligible patients, real-world evidence on the effectiveness of bortezomib maintenance following standard VMP induction is needed to guide post-induction treatment strategies in these settings. To address this gap, we conducted a multicenter retrospective study using a target trial emulation framework to evaluate the effectiveness of bortezomib maintenance in transplant-ineligible NDMM patients who achieved disease control after VMP induction, providing evidence to guide treatment decisions in real-world clinical practice where VMP-based regimens remain standard therapy.

Method

Study design

We conducted a comparative effectiveness analysis to evaluate bortezomib MT in transplant-ineligible patients with NDMM who completed 9 cycles of VMP induction. The intervention cohort comprised participants from a prospective single-arm clinical trial (Korean Multiple Myeloma Working Party; KMMWP-174). To address the limitations of single-arm design, we incorporated a control cohort using target trial emulation methodology applied to a multicenter registry database. The external control cohort was derived from the Catholic Research Network for Multiple Myeloma (CAREMM) registry, a multicenter database of university-affiliated hospitals. Control patients met all prospective trial eligibility criteria: completed 9 VMP cycles without progression, remained progression-free for at least 60 days post-VMP, and received no MT.

The primary aim of the study was to compare PFS between MT and control groups after 1:1 propensity score matching (PSM). To mitigate immortal time bias, we implemented a 60-day landmark analysis. The index date was defined as maintenance initiation for the intervention cohort and day 60 post-VMP for controls, reflecting the prospective trial's actual enrollment window. Primary analyses employed matching based on sex, age, type of myeloma, International Staging System (ISS), estimated glomerular filtration rate (eGFR), cytogenetic profile, and VMP response. We performed 3 sensitivity analyses: (1) alternative landmark analyses at 30 and 90 days, (2) multivariable Cox regression using the entire unmatched cohort adjusting for all propensity score variables, and (3) E-value calculations to assess unmeasured confounding. The complete target trial emulation framework is detailed in Supplementary Table 1.

Because the incidence of adverse events (AEs) in the two cohorts was collected during fundamentally different treatment phases (the control cohort received VMP induction therapy, while the case cohort received MT), a scientific comparison of AEs was not methodologically appropriate.

Therefore, AEs were summarized descriptively, and frequency of grade≥3 AEs in each cohort prior to PSM was reported.

The study protocol received approval from institutional review boards at all participating sites with waiver of informed consent for registry patients (lead IRB: XC23RIDI0066). Trial participants provided written informed consent. The study adhered to Declaration of Helsinki principles.

Study population

Between May 2017 and December 2021, the KMMWP-174 trial enrolled 78 patients, with 60 completing 9 VMP cycles and comprising the intervention cohort. From the CAREMM registry, we identified 644 transplant-ineligible NDMM patients treated between May 2010 and December 2024. Of 483 patients receiving first-line VMP, 118 met eligibility criteria for the control cohort after excluding: 327 who did not complete 9 VMP cycles, 7 who failed to achieve partial response (PR), 13 enrolled in KMMWP-174, and 18 who progressed or died within 60 days post-VMP. After 1:1 PSM, 54 patients from each cohort (total $N=108$) were included in the primary analysis (Fig. 1). Baseline characteristics were well-balanced between matched cohorts.

Treatment procedure with bortezomib

Bortezomib MT was administered subcutaneously at 1.3 mg/m² once weekly for 3 weeks (days 1, 8, 15) followed by a 1-week rest period in 28-day cycles [16]. Treatment continued until disease progression or completion of the planned 24-month protocol period.

Definitions

Disease staging followed the International Staging System (ISS) criteria [17]. High-risk cytogenetic abnormalities were defined as presence of del(17p), t(4;14), or t(14;16) detected by fluorescence in situ hybridization [18]. Renal function was evaluated using estimated glomerular filtration rate (eGFR) calculated with the Modification of Diet in Renal Disease (MDRD) formula [19]. Treatment responses were assessed according to International Myeloma Working Group (IMWG) 2016 consensus criteria [20]. OS was measured from the index date to death from any cause or last follow-up. PFS was measured from the index date to disease progression or death, whichever occurred first. The index date was defined as MT initiation for the intervention cohort and day 60 post-VMP completion for the control cohort, as specified in the study design. Severity of AEs was assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [21].

Statistical analysis

Baseline characteristics were compared using Mann-Whitney U test for continuous variables and chi-square test for categorical variables. We performed 1:1 PSM using logistic regression incorporating sex, age, type of myeloma, ISS,

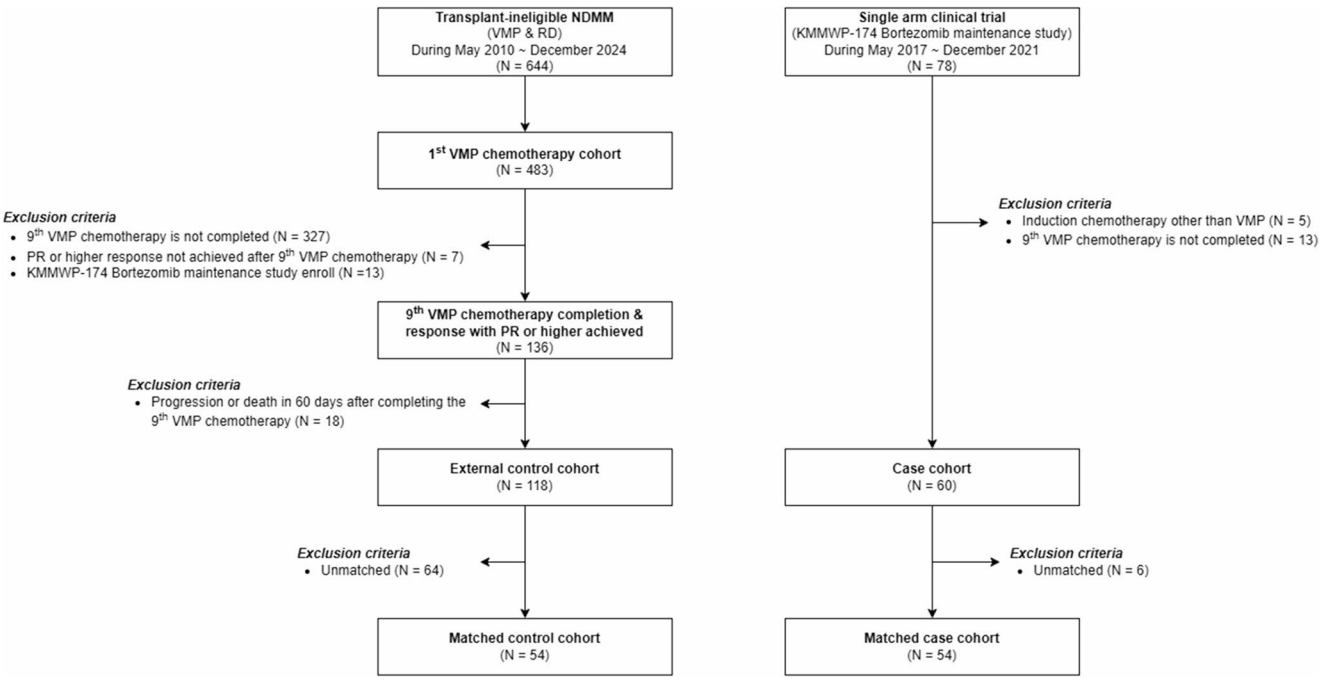

Fig. 1 Flowchart for study population selection. Abbreviations) NDMM, newly diagnosed multiple myeloma; PR, partial response

eGFR, cytogenetic profile, and VMP response. A caliper width of 0.25 standard deviations of the logit-transformed propensity score was applied to optimize covariate balance. Standardized mean differences (SMD) assessed matching quality, with SMD < 0.2 indicating adequate balance. Survival outcomes were estimated using Kaplan-Meier methods and compared with log-rank tests. Cox proportional hazards models calculated hazard ratios (HR) with 95% confidence intervals. Variables with SMD > 0.2 after matching underwent additional adjustment in Cox models. Subgroup analyses examined treatment effects across all matching variables except eGFR. To evaluate robustness against unmeasured confounding, we calculated E-values for observed hazard ratios following VanderWeele's methodology (PMID: 28693043). Statistical significance was set at two-sided $P < 0.05$. All analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Result

Baseline characteristics

After 1:1 PSM, 54 patients in each cohort were analyzed. All covariates achieved adequate balance (Supplementary Fig. 1). Table 1 presents baseline characteristics of the matched cohorts. No significant differences were observed in sex, age, heavy- and light-chain isotypes, ISS stage, β2-microglobulin, albumin, neutrophil count, or platelet count between groups (all $P > 0.05$). The case cohort had higher mean hemoglobin levels (11.41 ± 1.18 vs. 9.50 ± 1.70 g/dL, $P < 0.001$) but lower absolute lymphocyte counts (0.96 ± 0.36 vs. 1.88 ± 0.82 × 10^9/L, $P < 0.001$) compared to controls. Lactate dehydrogenase (LDH) levels exceeding the upper limit of normal were more frequent in the case cohort (55.6% vs. 29.6%, $P = 0.018$). Renal function was comparable between groups, with preserved eGFR (≥60 mL/min/1.73 m^2) in 63.0% of case patients, compared to 57.4% of controls ($P = 0.808$). Cytogenetic risk distribution showed no significant difference, though high-risk abnormalities were slightly more prevalent in the case cohort (25.9% vs. 22.2%, $P = 0.834$). Response to VMP induction was similar between groups: very good partial response (VGPR) rates were 44.4% versus 40.7%, and complete response (CR)/stringent CR (sCR) rates were identical at 25.9% ($P = 0.903$). Among all eligible patients before matching, the case cohort ($N = 60$) had a median follow-up of 51.5 months (95% CI: 44.8–61.5), while the control cohort ($N = 118$) had 72.0 months (95% CI: 68.8-NA; Supplementary Table 2).

In the case cohort, median treatment duration was 9 cycles (range: 1–26). Fifteen patients (25.0%) completed the planned 24-month protocol. Treatment discontinuation occurred in 45 patients (75.0%), primarily due to disease progression ($N = 37$, 61.7%) or withdrawal of consent ($N = 7$, 11.7%). One additional patient discontinued for other reasons. These findings reflect real-world treatment patterns in transplant-ineligible MM patients receiving MT.

Primary analysis: matched cohort outcomes

Bortezomib maintenance significantly improved PFS compared to observation. Median PFS was 26.5 months (95% CI: 21.9–32.2) in the case cohort versus 8.8 months (95% CI: 3.7–16.5) in the control cohort (HR 0.437, 95% CI: 0.292–0.653, $P < 0.001$; Fig. 2B). This benefit persisted over extended follow-up, with 3-year PFS rates of 33.2% versus 13.4% ($P < 0.001$) and 6-year PFS rates of 17.0% versus 5.4% ($P < 0.001$), respectively. Overall survival showed favorable trends without reaching statistical significance. Median OS was not reached in the case cohort (HR 0.703, 95% CI: 0.385–1.284, $P = 0.252$; Fig. 2A). The 3-year OS rates were 81.9% (95% CI: 71.8–93.4%) for case versus 70.8% (95% CI: 59.4–84.4%) for control ($P = 0.195$), with 6-year rates of 54.6% (95% CI: 39.0-76.5%) versus 44.5% (95% CI: 31.4–63.1%), respectively ($P = 0.118$).

Subgroup analyses revealed consistent PFS benefits across all patient subsets (Fig. 3). Significant improvements occurred regardless of sex (males: HR 0.333, 95% CI: 0.177–0.627; females: HR 0.071, 95% CI: 0.020–0.248), age ≥ 70 years (HR 0.321, 95% CI: 0.191–0.539), immunoglobulin type (IgG: HR 0.420, 95% CI: 0.232–0.761; non-IgG: HR 0.410, 95% CI: 0.197–0.854), ISS stage 2–3 (HR 0.352, 95% CI: 0.206–0.603), cytogenetic risk (standard: HR 0.228, 95% CI: 0.062–0.839; high-risk: HR 0.260, 95% CI: 0.091–0.742), and depth of response (PR/VGPR: HR 0.437, 95% CI: 0.269–0.708; CR/sCR: HR 0.159, 95% CI: 0.049–0.512). Overall survival benefits were limited to female patients (HR 0.123, 95% CI: 0.018–0.864) and ISS stage 1 (HR 0.001, 95% CI: 0.000-0.292; Supplementary Fig. 2).

Adverse events prior to PSM

Grade ≥ 3 AEs occurred in 37 patients (31.4%) in the control and 11 patients (18.7%) in the case cohorts, respectively, prior to PSM (Table 3). The most common grade ≥ 3 AEs were fever/neutropenic fever (9.3%) and anorexia (5.9%) in controls, while enterocolitis (5.1%) was most frequently observed in cases. No grade ≥ 3 PN was observed in either cohort.

Table 1 Baseline characteristics of patients after propensity score matching

Characteristic	Overall (*N*=108)	Control (*N*=54)	Case (*N*=54)	*P*-value
Median follow up, months (95% CI)	60.7 (53.6, 66.9)	69.2 (62.7, NA)	53.6 (46.2, 62.5)	<0.001
Sex, n (%)				0.842
Male	68 (63.0%)	35 (64.8%)	33 (61.1%)	
Female	40 (37.0%)	19 (35.2%)	21 (38.9%)	
Age, n (%)				0.673
<70	33 (30.6%)	16 (29.6%)	17 (31.5%)	
70–74	47 (43.5%)	22 (40.7%)	25 (46.3%)	
≥ 75	28 (25.9%)	16 (29.6%)	12 (22.2%)	
Heavy chain type, n (%)				1.000
IgG	61 (56.5%)	30 (55.6%)	31 (57.4%)	
Non-IgG	47 (43.5%)	24 (44.4%)	23 (42.6%)	
Light chain type, n (%)				0.601
Kappa	55 (50.9%)	27 (50.0%)	28 (51.9%)	
Lambda	52 (48.1%)	26 (48.1%)	26 (48.1%)	
Unknown	1 (0.9%)	1 (1.9%)	0 (0.0%)	
ISS stage, n (%)				0.659
I	30 (27.8%)	15 (27.8%)	15 (27.8%)	
II	34 (31.5%)	15 (27.8%)	19 (35.2%)	
III	44 (40.7%)	24 (44.4%)	20 (37.0%)	
β^2-microglobulin, mg/L, mean (SD)	6.89 (6.29)	6.83 (6.39)	6.94 (6.27)	0.924
Albumin, g/dL, mean (SD)	3.53 (0.64)	3.42 (0.60)	3.63 (0.66)	0.081
Lactate dehydrogenase ≥ ULN, n (%)	46 (42.6%)	16 (29.6%)	30 (55.6%)	0.018
Hemoglobin, g/dL, mean (SD)	10.46 (1.75)	9.50 (1.70)	11.41 (1.18)	<0.001
Absolute neutrophil count, x 10^9, mean (SD)	2.90 (1.11)	2.89 (1.17)	2.91 (1.05)	0.927
Absolute lymphocyte count, x 10^9, mean (SD)	1.41 (0.78)	1.88 (0.82)	0.96 (0.36)	<0.001
Platelet count, x 10^9/L, mean (SD)	188.67 (66.01)	197.34 (74.29)	180.17 (56.13)	0.180
eGFR, mL/min/1.73m^2, n (%)				0.808
<30	16 (14.8%)	9 (16.7%)	7 (13.0%)	
<30–59	27 (25.0%)	14 (25.9%)	13 (24.1%)	
≥ 60	65 (60.2%)	31 (57.4%)	34 (63.0%)	
Cytogenetic abnormalities, n (%)				0.834
Standard risk	31 (28.7%)	15 (27.8%)	16 (29.6%)	
High risk	26 (24.1%)	12 (22.2%)	14 (25.9%)	
Unknown	51 (47.2%)	27 (50.0%)	24 (44.4%)	
VMP induction response, n (%)				0.903
PR	34 (31.5%)	18 (33.3%)	16 (29.6%)	
VGPR	46 (42.6%)	22 (40.7%)	24 (44.4%)	
CR/sCR	28 (25.9%)	14 (25.9%)	14 (25.9%)	

CI confidence interval, *Ig* immunoglobulin, *SD* standard deviation, *IU* international unit, *ULN* upper limit of normal, *eGFR* estimated glomerular filtration rate, *PR* partial response, *VGPR* very good partial response, *CR/sCR* complete response/stringent complete response

Sensitivity and supplementary analyses

Unmatched cohort analysis

To validate our findings in the broader eligible population, multivariable Cox regression was performed using all 178 patients (Table 2). After adjusting for baseline covariates, bortezomib maintenance remained significantly associated with improved PFS (HR 0.400, 95% CI: 0.268–0.596, $P<0.001$), consistent with the matched analysis. No significant association with OS was observed (HR 0.735, 95% CI: 0.409–1.324, $P=0.306$). Among other covariates, depth of response to VMP induction emerged as an independent prognostic factor, with VGPR (HR 0.557, 95% CI: 0.360–0.862, $P=0.009$) and CR/sCR (HR 0.363, 95% CI: 0.224–0.588, $P<0.001$) associated with significantly reduced PFS risk compared to PR. Other baseline characteristics including sex, age, heavy chain type, ISS stage, and cytogenetic risk were not independently associated with survival outcomes.

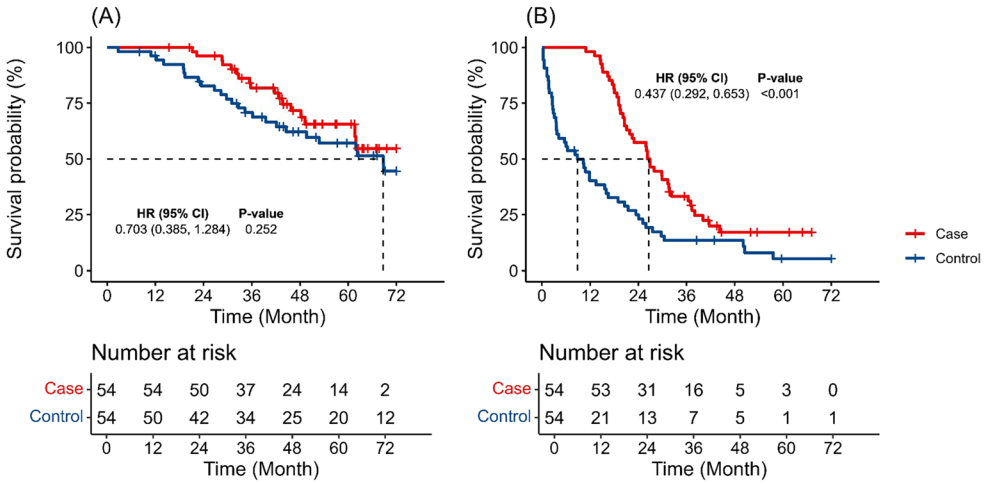

Fig. 2 Comparative survival analysis of matched cases (red line) and matched controls (blue line) (**A**) overall survival and (**B**) progression-free survival. Abbreviations) HR, Hazard ratio; CI, Confidence interval

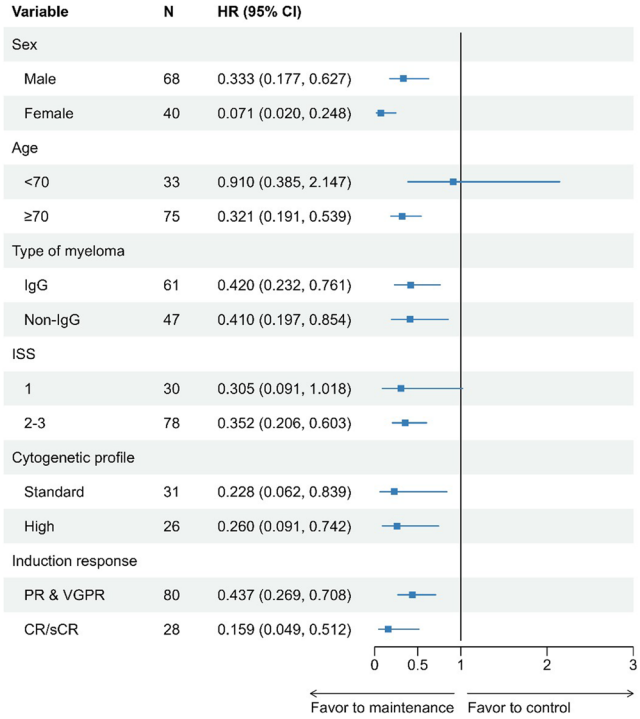

Fig. 3 Forest plot comparing progression-free survival of each cohort. Abbreviations) HR, hazard ratio; CI, confidence interval

Robustness checks

The PFS benefit remained consistent across different follow-up periods and alternative eligibility criteria (Supplementary Table 3). E-value analysis for unmeasured confounding yielded a value of 2.93 for the observed HR of 0.437, indicating that an unmeasured confounder would require risk ratio associations of at least 2.93 with both treatment assignment and PFS to nullify our findings. Even at the upper confidence limit (HR 0.653), the E-value remained substantial at 2.02, suggesting that only relatively strong unmeasured confounders—not modest confounding—could explain away the observed treatment effect. These sensitivity analyses provide robust evidence supporting the protective effect

Table 2 Frequency of grade 3 or 4 adverse events prior to propensity score matching

Variables	Control cohort (*N*=118)	Case cohort (*N*=60)
Total events, n (%)	37 (31.4%)	11 (18.7%)
Hematologic toxicities		
Neutropenia	-	-
Lymphopenia	-	-
Thrombocytopenia	-	1 (1.7%)
Anemia	-	1 (1.7%)
Gastrointestinal toxicities		
Anorexia	7 (5.9%)	-
GERD	-	1 (1.7%)
Nausea and vomiting	-	1 (1.7%)
Infectious complications		
Chilling	2 (1.6%)	-
Pneumonia	2 (1.6%)	1 (1.7%)
Enterocolitis	2 (1.6%)	3 (5.1%)
Herpes zoster	1 (0.8%)	-
Septic shock	1 (0.8%)	-
Acute pyelonephritis	1 (0.8%)	-
Fever / Neutropenic fever	11 (9.3%)	-
Neurologic toxicities		
Anxiety	1 (0.8%)	-
Dizziness	2 (1.6%)	-
Headache	1 (0.8%)	-
Peripheral neuropathy	-	-
Other toxicities		
Pain	2 (1.6%)	-
Rash	-	1 (1.7%)
Fatigue	2 (1.6%)	1 (1.7%)
Hypoglycemia	1 (0.8%)	-
Hyperglycemia	1 (0.8%)	-
Operation due to trigger finger	-	1 (1.7%)

GERD gastro-esophageal reflux disease

Table 3 Multivariate analysis of factors associated with survival outcomes

Variables	Overall survival (OS)		Progression-free survival (PFS)	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Cohort				
Control (*N* = 118)	1		1	
Case (*N* = 60)	0.735 (0.409, 1.324)	0.306	0.400 (0.268, 0.596)	< 0.001
Sex				
Male	1		1	
Female	0.907 (0.533, 1.546)	0.720	1.113 (0.777, 1.593)	0.561
Age				
< 70	1		1	
70–74	1.317 (0.725, 2.394)	0.366	1.339 (0.891, 2.013)	0.160
≥ 75	1.234 (0.632, 2.411)	0.537	0.892 (0.563, 1.413)	0.627
Heavy chain type				
Non-IgG	1		1	
IgG	0.935 (0.542, 1.614)	0.809	0.921 (0.630, 1.347)	0.671
ISS stage				
I	1		1	
II	1.111 (0.551, 2.240)	0.768	0.753 (0.475, 1.193)	0.227
III	1.165 (0.512, 2.651)	0.716	0.875 (0.528, 1.452)	0.606
eGFR, mL/min/1.73m^2				
<30	1		1	
<30–59	1.064 (0.474, 2.389)	0.880	2.043 (1.144, 3.648)	0.016
≥ 60	0.897 (0.383, 2.104)	0.803	1.463 (0.826, 2.589)	0.192
Cytogenetic abnormalities				
Standard risk	1		1	
High risk	1.729 (0.883, 3.383)	0.110	1.280 (0.781, 2.096)	0.327
Unknown	0.900 (0.493, 1.642)	0.731	0.965 (0.648, 1.439)	0.863
VMP induction response				
PR	1		1	
VGPR	0.771 (0.389, 1.527)	0.456	0.557 (0.360, 0.862)	0.009
CR/sCR	0.845 (0.415, 1.724)	0.644	0.363 (0.224, 0.588)	< 0.001

Abbreviations) *CI* confidence interval, *Ig* immunoglobulin, *SD* standard deviation, *eGFR* estimated glomerular filtration rate, *PR* partial response, *VGPR* very good partial response, *CR/sCR* complete response/stringent complete response

of bortezomib maintenance on PFS in transplant-ineligible NDMM patients.

Discussion

This multicenter study employing target trial emulation framework demonstrates that bortezomib maintenance following VMP induction significantly prolongs PFS in transplant-ineligible NDMM patients. The magnitude of PFS benefit (HR 0.437) and its consistency across clinically relevant subgroups—including elderly patients, those with ISS stage II-III disease, and those with high-risk cytogenetic abnormalities—establish the clinical value of PI-based maintenance. While lenalidomide-based or monoclonal antibody-containing regimens have emerged as preferred options for transplant-ineligible patients [22–26], substantial variability in drug availability, reimbursement policies, and patient comorbidities continues to shape treatment selection across diverse healthcare settings. In Korea, VMP continues to be frequently used, particularly for elderly patients and those with renal impairment or elevated thrombotic risk, for whom lenalidomide-based triplets may be contraindicated or less feasible. Our study provides outcome benchmarks relevant to such populations, offering practical evidence for bortezomib maintenance as an accessible post-induction strategy in resource-constrained settings.

Our findings align with landmark trials investigating bortezomib-containing maintenance regimens. The GEM-2005MAS65 [5] and GIMEMA-MM-03-05 [27] studies demonstrated significant survival benefits with ongoing proteasome inhibition (median PFS: 35.3 vs. 24.8 months, HR 0.58; 5-year OS: 61% vs. 51%, HR 0.70). The 18-month PFS improvement observed in our predominantly elderly cohort (65.8% ≥ 70 years) is particularly noteworthy given limited therapeutic options and poorer outcomes in this vulnerable population. Age-stratified analyses revealed differential benefits (Supplementary Tables 4, 5): while patients ≥ 70 years derived clear benefit from maintenance, treatment effects appeared less pronounced in younger patients (< 70 years, *N* = 33), likely reflecting biological heterogeneity, small sample size, and limited statistical power. These findings emphasize tailoring maintenance strategies to patient characteristics and clinical context.

The unmatched multivariable analysis further validates the robustness of our findings, demonstrating consistent treatment effects (HR 0.400, 95% CI: 0.268–0.596) when evaluated within the broader eligible population. Notably, depth of response to VMP induction emerged as a strong independent prognostic factor, with CR/sCR patients showing superior PFS compared to PR (HR 0.363, 95% CI: 0.224–0.588). This reinforces that MT may be particularly valuable in sustaining and potentially deepening remissions achieved during induction, thereby delaying relapse and preserving organ function.

The observed median PFS of 8.8 months in our control cohort requires careful interpretation within our study design context. Our stringent eligibility criteria—completion of all 9 VMP cycles, achievement of at least PR, and 60-day progression-free status—selected a specific subpopulation distinct from intention-to-treat populations in randomized trials. This selection process excludes patients who progressed early, potentially enriching for a cohort at higher risk once active therapy ceased. Additionally, the 60-day landmark analysis, while essential for eliminating immortal time bias, creates a distinct analytical timeframe compared to trials measuring PFS from treatment initiation. Real-world registry data also capture greater clinical heterogeneity than controlled trials, with our cohort including 30% with renal impairment and 66% aged≥70 years—populations often underrepresented in prospective trials. The decision to discontinue therapy after VMP may itself reflect unmeasured clinical factors such as treatment tolerance or physician assessment. However, our comprehensive sensitivity analyses support treatment effect robustness. The E-value of 2.93 indicates that an unmeasured confounder would need to be associated with both treatment assignment and PFS by nearly 3-fold to fully explain our observed HR of 0.437. Furthermore, consistent treatment effects across alternative landmark definitions (30, 60, and 90 days) and multivariable regression in the full cohort (HR 0.400, $P<0.001$) validate our findings. Clinically, what matters most is the relative treatment effect—the 18-month PFS improvement—rather than absolute values, with this substantial benefit consistent across high-risk subgroups.

Beyond addressing methodological concerns, our study demonstrates the value of target trial emulation in hematologic malignancy research. This causal inference framework, increasingly recognized in cardiology and infectious diseases, remains underutilized in myeloma despite its potential to generate robust evidence when randomized trials are infeasible. The convergence of results across multiple analytical approaches—PSM, landmark analyses, multivariable regression, and E-value assessment—strengthens confidence beyond what any single analysis could provide, offering a replicable template for future comparative effectiveness studies.

The safety profile requires careful interpretation given that AEs were collected during different treatment phases. Distinct toxicity patterns emerged: the control cohort predominantly experienced infectious events during intensive VMP induction, whereas the case cohort showed primarily GI toxicity with lower rates of infections. Notably, no grade ≥ 3 PN was observed in either cohort. While bortezomib-associated PN remains a concern in MT, the absence of severe neuropathy may reflect strict eligibility criteria (baseline PN grade ≤ 1), weekly subcutaneous administration [14, 28], and proactive dose modifications [29–31]. These findings support feasibility of bortezomib maintenance in elderly, transplant-ineligible patients with appropriate patient selection and monitoring.

The clinical relevance extends beyond settings where VMP remains first-line due to economic constraints. Patient-specific factors mandate VMP-based approaches even in resource-rich environments. Renal impairment, present in approximately 50% of newly diagnosed patients, contraindicates or requires significant lenalidomide dose reduction due to renal excretion and toxicity risk [32, 33]. Elderly patients with comorbidities may be unsuitable for intensive triplet regimens. Our study addresses whether proteasome inhibitor continuation after VMP provides benefit over observation—a question remaining relevant independent of whether VMP represents optimal initial therapy. This applies to healthcare systems globally where VMP continues as standard practice due to economic disparities (lifetime costs differing by over $300,000 between VMP and contemporary regimens), regulatory timelines, or patient-specific contraindications [34]. The substantial treatment effect establishes comparative benchmarks for evaluating emerging maintenance strategies across diverse contexts.

This study has several limitations inherent to its retrospective design. First, despite rigorous PSM and comprehensive sensitivity analyses, our retrospective design cannot completely eliminate the possibility of unmeasured confounding. Second, the study population comprised patients who successfully completed 9 VMP cycles and remained progression-free for 60 days, potentially limiting generalizability to less selected or intention-to-treat populations. Third, the control group's shorter median PFS, while reflecting real-world practice patterns and our specific eligibility criteria including the 60-day landmark analysis, may limit direct comparisons with published trial data that measure outcomes from treatment initiation. Fourth, data collection predated widespread adoption of contemporary lenalidomide- or daratumumab-based triplet regimens; however, this does not diminish the relevance of our findings for settings where VMP remains standard therapy due to economic, regulatory, or patient-specific factors. Fifth, AEs assessment based on retrospective chart review rather than

standardized prospective scales may have underestimated toxicity severity, particularly for subjective symptoms such as PN or fatigue. Finally, we lacked systematic assessments of minimal residual disease and QoL outcomes, which are increasingly recognized as important endpoints for evaluating maintenance therapy benefits beyond survival metrics.

In conclusion, this multicenter study demonstrates that bortezomib maintenance following VMP induction significantly prolongs progression-free survival in transplant-ineligible NDMM patients, with benefits consistent across elderly and high-risk subgroups. The convergence of findings across propensity score matching, alternative landmark analyses, and E-value assessment strengthens confidence in these results despite the observational design. Weekly subcutaneous bortezomib administration demonstrated acceptable tolerability, supporting the feasibility of proteasome inhibitor-based maintenance in real-world practice. These findings provide actionable evidence for healthcare settings where VMP remains standard therapy due to economic constraints, regulatory factors, or patient-specific contraindications such as renal impairment. This study also demonstrates the value of target trial emulation in generating robust comparative effectiveness evidence from observational data. Future research should incorporate minimal residual disease monitoring, QoL assessments, and direct comparisons with contemporary maintenance approaches to optimize treatment strategies for this vulnerable population.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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