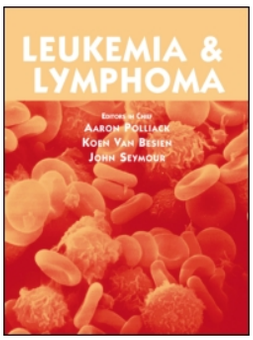

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ORIGINAL ARTICLE

The effects of different schedules of bortezomib, melphalan, and prednisone for patients with newly diagnosed multiple myeloma who are transplant ineligible: a matching-adjusted indirect comparison

Maria-Victoria Mateos[a], Jesus San-Miguel[b], Hartmut Goldschmidt[c], Pieter Sonneveld[d], Meletios A. Dimopoulos[e], Bart Heeg[f], Mahmoud Hashim[f], William Deraedt[g], Peter Hu[h], Annette Lam[i] and Jianming He[i]

[a]Haematology Department, University Hospital of Salamanca/IBSAL, Salamanca, Spain; [b]Clínica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Pamplona, Spain; [c]Internal Medicine V and National Center of Tumor Diseases (NCT), University Clinic Heidelberg, Heidelberg, Germany; [d]Department of Haematology, Erasmus MC, Rotterdam, The Netherlands; [e]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece; [f]Ingress Health, Rotterdam, The Netherlands; [g]Oncology R&D, Janssen Research & Development, Beerse, Belgium; [h]Statistical Programming (Haematology), Janssen Research & Development, LLC, Raritan, NJ, USA; [i]Global Market Access and Health Policy, Janssen Global Services, LLC, Raritan, NJ, USA

ABSTRACT

For patients with newly diagnosed multiple myeloma (NDMM) who are transplant ineligible, bortezomib-melphalan-prednisone (VMP) demonstrated superior efficacy based on the VISTA trial. In subsequent trials, twice-weekly bortezomib was limited to the first cycle or completely replaced with once-weekly bortezomib to reduce toxicity. Following a systematic literature review, the efficacy and safety of modified VMP schedules (pooled data from the once-weekly bortezomib VMP arm of the GIMEMA trial and the VMP arm of the ALCYONE trial) were compared to the VISTA schedule using naïve and unanchored matching-adjusted indirect comparison (MAIC). Median progression-free survival was similar between VISTA and modified VMP (20.7 months [95% CI, 18.4–24.3] vs 19.6 months [95% CI, 18.8–21.0]). Peripheral neuropathy was significantly reduced with modified VMP versus VISTA VMP (all grades: naïve, 32.1% vs 46.8% and MAIC, 32.1% vs 46.7%; both $p < .0001$). These findings support a modified VMP dosing schedule for patients with NDMM who are transplant ineligible.

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VMP; multiple myeloma; matching-adjusted indirect comparison

Introduction

Multiple myeloma (MM) is primarily a disease of older individuals, with a median age of 69 years at diagnosis [1,2]. With the introduction of agents such as proteasome inhibitors and immunomodulatory drugs, the 5-year survival rates of MM have increased substantially over the last few decades, from 29.8% in 1990 to 34.5% in 2000 and to 52.7% in 2009, although outcomes remain poor [3–5]. A plethora of combination regimens exist in the current treatment landscape for newly diagnosed MM (NDMM), and a major factor that guides treatment recommendations for NDMM is the ability of the patient to undergo high-dose chemotherapy followed by autologous stem cell transplant, which is dependent on the patient's age and/or comorbidities [6–8].

Bortezomib, melphalan, and prednisone (VMP) is a standard-of-care regimen outside of the United States for patients with NDMM who are transplant ineligible; however, with the approved schedule, substantial toxicity, particularly peripheral neuropathy, leads to dose reductions or premature treatment discontinuation [9,10]. For patients with NDMM who are transplant ineligible, the efficacy of VMP was established in the phase 3 VISTA trial [9,11–14]. The VISTA trial used a VMP dosing schedule of twice-weekly dosing for four 6-week cycles followed by once-weekly (QW) dosing for five 6-week cycles [9,12]. A significant improvement in efficacy was demonstrated with the addition of bortezomib to melphalan-prednisone (MP), with a median time to progression of 20.7 months for those receiving VMP and 15.0 months for those receiving MP (hazard ratio [HR], 0.540; 95% confidence interval [CI], 0.417–0.699; $p < .001$) [9]. Significant results were also observed for key secondary endpoints, including progression-free survival (PFS), overall response rate (ORR), and complete response (CR) rate [9]. The triplet combination was associated with more toxicity,

CONTACT Jianming He JHe2@its.jnj.com Janssen Global Services, LLC, 1000 US Route 202 South, Raritan, NJ 08869, USA

particularly a higher rate of peripheral neuropathy (VMP, 44% vs MP, 5%) [9]. The duration of therapy and cumulative dose of bortezomib have been shown to contribute to the occurrence of peripheral neuropathy [15]; for most patients, peripheral neuropathy resolves or improves after dose modification of bortezomib or completion of therapy [15–17].

To reduce toxicity of VMP, twice-weekly bortezomib was limited to the first cycle or completely replaced with QW bortezomib in subsequent VMP-based trials (Table 1), including GIMEMA [Gruppo Italiano Malattie Ematologiche dell'Adulto], PETHEMA/GEM05 by the Spanish Myeloma Group, and ALCYONE [18–20]. Moreover, recent guidelines have recommended a less intensive VMP schedule [7].

In the absence of clinical trials directly comparing the VISTA VMP dosage regimen with modified VMP regimens, a matching-adjusted indirect comparison (MAIC) provides a means to compare absolute treatment effects across diverse populations. This statistical approach uses individual patient data from one comparison arm to decrease the risk of bias associated with a naïve indirect comparison of studies that enroll different patient populations and employ different relative effect measures [21,22]. The MAIC method uses individual patient data to re-weight the population and matches the baseline characteristics of the population of the other comparison arm for which only aggregate results are available. This technique has been used increasingly more often and across a wide variety of therapeutic areas to compare clinical efficacy and inform cost-effectiveness decisions [23–27]. Furthermore, an unanchored MAIC can be conducted, allowing adjustment for cross-trial differences across single-arm trials or trials without a common comparator, such as in oncology trials for patients with poor prognosis and in which the ability to "anchor" treatments to a placebo arm does not exist [21,28].

Here, we report the efficacy and safety of a modified dosing schedule of bortezomib in VMP-based regimens versus the dosing schedule established in VISTA for patients with NDMM who are transplant ineligible.

Materials and methods

Systematic literature review

A systematic literature review of PubMed, Embase, and Cochrane databases was conducted in July 2019 for conference abstracts published from 2012 onwards and other peer-reviewed reports published prior to July 2019, without time limitation. Eligible publications were from randomized controlled trials investigating systemic treatments (including VMP) in patients with NDMM who were transplant ineligible. The search revealed 85 publications pertaining to 35 trials, of which 18 publications provided data from 8 clinical trials evaluating VMP as an active or control treatment. Of these, the GIMEMA MM-03-05 (GIMEMA-QW) [19,29,30], PETHEMA/GEM05 [18,31], ALCYONE [20]

Table 1. VMP dosing schedules in the original VISTA trial and trials of the modified regimen.

		Modified VMP dosing schedules		
	VISTA ($N = 682$)	ALCYONE ($N = 706$)	GIMEMA ($N = 511$)	PETHEMA/GEM05 ($N = 260$)
Trial design	Randomized, open-label, phase 3 VMP vs MP	Randomized, open-label, active-controlled, phase 3 Daratumumab-VMP vs VMP	Randomized, open-label, phase 3 VMPT vs VMP, maintenance VT in VMPT arm	Phase 3 VMP vs VTP followed by maintenance VP vs VT
Total cycles	Nine 6-week cycles (54 weeks)	Nine 6-week cycles (54 weeks)	Nine 5-week cycles (45 weeks); maintenance for up to 2 years	One 6-week cycle, five 5-week cycles (31 weeks); maintenance for up to 3 years
Bortezomib	Cycles 1–4: 1.3 mg/m^2 IV Days 1, 4, 8, 11, 22, 25, 29, and 32 (twice weekly for Weeks 1, 2, 4, and 5) Cycles 5–9: 1.3 mg/m^2 IV Days 1, 8, 22, and 29 (QW for Weeks 1, 2, 4, and 5)	Cycle 1: 1.3 mg/m^2 SC Days 1, 4, 8, 11, 22, 25, 29, and 32 (twice weekly for Weeks 1, 2, 4, and 5) Cycles 2–9: 1.3 mg/m^2 SC Days 1, 8, 22, and 29 (QW for Weeks 1, 2, 4, and 5)	Cycles 1–9: 1.3 mg/m^2 IV Days 1, 8, 15, and 22 (QW for Weeks 1–4)	Cycle 1: 1.3 mg/m^2 IV Days 1, 4, 8, 11, 22, 25, 29, and 32 (twice weekly for Weeks 1, 2, 4, and 5) Cycles 2–6: 1.3 mg/m^2 IV Days 1, 8, 15, and 22 (QW for Weeks 1–4)
Melphalan	All studies: 9 mg/m^2 orally Days 1–4 all cycles			
Prednisone	All studies: 60 mg/m^2 orally Days 1–4 all cycles			

IV: intravenous; QW: once weekly; SC: subcutaneous; T: thalidomide; VMP: bortezomib/melphalan/prednisone; VP: bortezomib/prednisone; VT: bortezomib/thalidomide; VTP: bortezomib/thalidomide/prednisone.

trials used a modified VMP dosing schedule (Table 1). In addition, a modified VMP dosing schedule was used in IMPROVE-MPB [32] but only a conference abstract, with limited data, was available. Therefore, this study was not included in the analysis. The phase 2 trial by San Miguel et al. [33], the phase 3 UPFRONT trial [34] and the phase 3 CLARION trial [35] used a VMP regimen similar to that used in the VISTA trial. Based on this systematic review, there were no pairwise comparisons between a modified VMP schedule and the VISTA VMP schedule for treatment of MM. As the San Miguel et al study [33], UPFRONT study [34] and CLARION trial [35] followed a VISTA-like regimen, and because individual patient data were not available, neither of these 3 studies were included in this analysis. To facilitate interpretation of results, a systematic literature search of PubMed was conducted for noninferiority margins in recent oncology clinical trials. The mean/median margins for PFS and ORR were 1.314/1.300 and 13%/15%, respectively.

Data pooling

Baseline characteristics were summarized using individual patient data from trial databases [10,20]. Efficacy and safety data were quantitatively compared between the VISTA VMP schedule and the pooled modified VMP schedules from ALCYONE, GIMEMA, and PETHEMA/GEM05. For the GIMEMA trial, only the QW schedule (Cycles 1–9) from GIMEMA-QW was used in all comparisons. Data from ALCYONE were based on a median follow-up of 27.8 months [36] and 25.9 months for VISTA [11].

Two sets of analyses were performed. The primary analysis was a comparison of modified VMP schedules pooled from the ALCYONE (which used a QW bortezomib dosing schedule during Cycles 2–9) and GIMEMA-QW trials versus VISTA. The PETHEMA/GEM05 modified VMP arm was excluded from the primary analysis because bortezomib-based maintenance after the VMP schedule was permitted, which could have impacted longer-term endpoints (eg, PFS). The sensitivity analysis was conducted to compare pooled modified VMP schedules from all 3 trials (ALCYONE, GIMEMA-QW, and PETHEMA/GEM05) versus the VISTA trial.

Individual patient data were obtained from the sponsor for the VISTA and ALCYONE trials. A published validated method was used to reconstruct individual patient data for PFS of the GIMEMA-QW and PETHEMA/GEM05 trials based on digitizing reported Kaplan-Meier curves [37]. As disease progression and response assessment for VISTA VMP was originally based on the European Society for Blood and Marrow Transplantation criteria [37], a post hoc analysis was applied using a computer algorithm to implement the International Myeloma Working Group criteria [38,39] in order to enable comparisons with the ALCYONE and GIMEMA trials. Additionally, PFS data from the VISTA trial at a median follow-up of 25.9 months was censored for subsequent therapy to match the definition of PFS used in ALCYONE.

Comparisons

A naïve comparison and an unanchored MAIC were performed for each analysis. The naïve comparison made no adjustments for patient-level data; outcomes observed with modified VMP schedules were compared to those of the VISTA VMP schedule directly. The MAIC was designed to weight individual patients in the VISTA VMP treatment arm to match the distribution statistics of the baseline characteristics to those in the pooled modified VMP treatment arms. Identified effect modifiers and prognostic factors included age, gender, International Staging System (ISS) stage, β2-microglobulin, albumin, serum creatinine, creatinine clearance, and cytogenetic risk profile; these variables were reported and extracted from a previous study [10]. For each patient in the VISTA VMP study, a weight was attached based on observed baseline characteristics, which was then used to calculate weighted outcomes [28]. The R code published by the National Institute for Health and Care Excellence (NICE) was used [28].

Statistical analysis

Outcomes considered in the analyses were PFS, ORR, rate of CR, and adverse events (AEs). For PFS, the null hypothesis of no difference was tested using a log-rank test. A Cox regression model was fitted with treatment arm identification as a stratification factor. The regression coefficient from the model provided estimates of HRs with 2-sided 95% CIs to compare VMP schedules. For ORR, CR, and AEs, rate differences were calculated with 2-sided 95% CIs to compare VMP schedules.

Results

Patients

A total of 344 patients received VMP in the VISTA trial and 356, 191, and 130 patients received modified VMP in the ALCYONE, GIMEMA-QW, and PETHEMA/GEM05

trials, respectively. Baseline demographics and clinical characteristics are provided in Table 2. The populations were generally similar. More patients in the GIMEMA-QW (29%) and PETHEMA/GEM05 (30%) trials had ISS stage I MM, compared with the VISTA (19%) and ALCYONE (19%) trials. Median albumin levels were balanced across the trials; however, GIMEMA-QW had fewer patients with albumin levels <35 g/L compared with the other trials. More patients in the GIMEMA-QW trial (24%) were identified with high-risk cytogenetics compared with the other trials. After matching for the unanchored MAIC, baseline demographics and clinical characteristics remained similar. Table 3 presents effective sample size (ESS) and summary statistics of individual weights after the MAIC.

Discontinuations of VMP due to AEs occurred in 14.7% of patients in the VISTA trial, with an additional 18.5% of patients selectively discontinuing bortezomib due to AEs in spite of the fact that discontinuation was not required according to its severity. [10]. Among patients who received the modified VMP regimen, discontinuations due to AEs occurred in 9.3%, 13.2%, and 12.0% of patients in the ALCYONE, GIMEMA-QW, and PETHEMA/GEM05 studies, respectively. Treatment-related deaths were lowest in the VISTA trial (2.0%) compared with 2.3% in ALCYONE and 4.0% in PETHEMA/GEM05. Treatment-related deaths were not reported in the GIMEMA-QW trial.

Bortezomib exposure

Patients in the VISTA and PETHEMA/GEM05 trials received a higher median cumulative dose of bortezomib (29.4 mg/m^2 and 32.9 mg/m^2, respectively) in early cycles (Cycles 1–4 for all studies except for PETHEMA/GEM05 [Cycles 1–6]) of treatment as compared to those in the ALCYONE and GIMEMA-QW trials (24.0 mg/m^2 and 20.8 mg/m^2, respectively). In later cycles (Cycles 5–9), the median cumulative dose was lower in the VISTA trial (15.6 mg/m^2) compared to the GIMEMA-QW and ALCYONE trials (23.4 mg/m^2 and 23.1 mg/m^2, respectively). As PETHEMA/GEM05 included only 6 induction cycles, the median cumulative dose for all cycles comprised Cycles 1 to 6 only and

Table 2. Summary of key demographic and baseline disease characteristics among subjects receiving VMP across the VISTA, ALCYONE, GIMEMA-QW, and PETHEMA/GEM05 Phase 3 Studies.

	VISTA ($n = 344$)	ALCYONE ($n = 356$)	GIMEMA-QW ($n = 191$)	PETHEMA/GEM05 ($n = 130$)
Median (range) age, years	71 (57–90)	71 (50–91)	71 (56–86)	72 (65–83)
Interquartile range	68–76	68–75	68–75	68–76
Age ≥75 years, *n* (%)	106 (31)	107 (30)	49 (26)	42 (32)
Male, *n* (%)	175 (51)	167 (47)	89 (47)	64 (49)
ISS stage, *n* (%)	*n* = 344	*n* = 356	*n* = 141	*n* = 130
I	64 (19)	67 (19)	41 (29)	39 (30)
II	161 (47)	160 (45)	62 (44)	51 (39)
III	119 (35)	129 (36)	38 (27)	40 (31)
β2-microglobulin (mg/L), *n*	344	356	149	128
Median (range)	4.2 (1.7–21.6)	4.6 (1.4–46.1)	3.9 (0.3–25.6)	3.8 (0.2–21.7)
Albumin (g/L), *n*	342	355	160	130
Median (range)	33 (13–47)	36 (12–49)	38 (13–50)	35.8 (20–50.5)
<35 g/L, n (%)	200 (58)	192 (54)	49 (31)	56 (43)
Creatinine (mol/L), *n*	344	356	191	130
Median (range)	93.9 (43–270)	81 (27.4–530)	76.3 (35.8–190.7)	76.3 (33.6–152.5)
Creatinine clearance <30 mL/min, *n* (%)	20 (6)	8 (2)	21 (11)	4 (3)
High risk cytogenetics: t(4;14), t(14;16), del(17p) by FISH, n/N (%)	26/168 (15)	45/302 (15)	33/140 (24)	22/113 (19)

FISH: fluorescence in situ hybridization; ISS: International Staging System; QW: once weekly; VMP: bortezomib-melphalan-prednisone.

Table 3. Effective sample size and summary statistics of individual weights after adjusting population for MAIC.

Endpoint	Response		Progression-free survival		Safety	
Analysis	Primary analysis	Sensitivity analysis	Primary analysis	Sensitivity analysis	Primary analysis	Sensitivity analysis
VISTA trial population, *n*	337	337	344	344	340	340
Effective sample size	124.3	113.9	114	114.5	124.5	114.2
Individual weights, summary statistics						
Minimum	0.075	0.075	0.073	0.073	0.073	0.073
1st Quartile	0.263	0.282	0.26	0.26	0.257	0.278
Median	0.561	0.516	0.567	0.521	0.57	0.522
Mean	1	1	1	1	1	1
3rd Quartile	1.454	1.279	1.367	1.23	1.439	1.247
Maximum	10.542	11.04	10.959	11.283	10.651	11.237

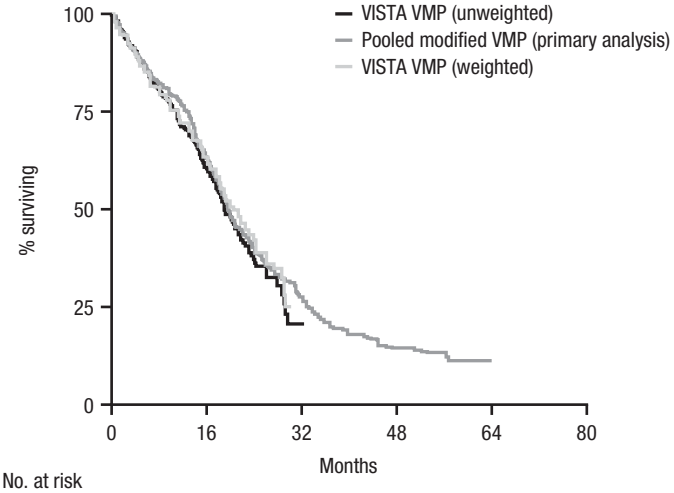
N: number of patients included in analysis.

was lower (32.9 mg/m^2) than that for the other 3 trials (VISTA, 38.5 mg/m^2; ALCYONE, 42.2 mg/m^2; GIMEMA-QW, 40.3 mg/m^2). The mean cumulative dose of bortezomib for all cycles was similar for both the primary (36.5 mg/m^2) and supplemental (35.0 mg/m^2) analyses and was similar to that of the VISTA trial (36.6 mg/m^2). The proportion of the planned bortezomib dose that was delivered with any VMP treatment was highest in the PETHEMA/GEM05 trial (90.4%) and GIMEMA-QW (86.1%) compared with ALCYONE (68.0%) and VISTA (57.0%) trials [10].

Efficacy

The analysis was based on data obtained after a comparable follow-up period for ALCYONE (27.8 months) and VISTA (25.9 months) [11]. The primary analysis of pooled data from GIMEMA-QW and ALCYONE trials versus the VISTA trial showed similar median PFS for both the naïve and the MAIC (Figure 1 and Table 4). There was no significant difference in median PFS between VISTA and GIMEMA-QW plus ALCYONE in the naïve comparison (19.1 months [95% CI, 17.8–21.6] versus 19.6 months [95% CI, 18.8–21.0]) or in the MAIC (20.7 months [95% CI, 18.4–24.3] versus 19.6 months [95% CI, 18.8–21.0]). Based on the mean noninferiority margin for PFS of 1.314, the GIMEMA-QW and ALCYONE pooled results were noninferior [40] to VISTA for PFS in the primary analysis (both naïve and MAIC comparisons). When compared to the median noninferiority margin (1.300), noninferiority can also be concluded. In the sensitivity analysis of GIMEMA-QW, ALCYONE, and PETHEMA/GEM05, pooled results were noninferior to VISTA for the naïve comparison and the MAIC, applying the same margin used for the primary analysis (Table 4). Kaplan-Meier plots of PFS for the 2 analyses are presented in Figure 1. Both sets of curves show overlap between VISTA (both naïve and MAIC) and the pooled modified VMP regimen data, suggesting no difference in treatment with regard to PFS.

CR rates were significantly higher for VISTA (naïve, 31.5%; MAIC, 35.4%) compared to the GIMEMA-QW and ALCYONE pooled data (24.6% for both comparisons; naïve, $p = .029$; MAIC, $p = .002$; Table 4). Similar results were observed with the sensitivity analysis, with CR rates of 31.5% and 35% for VISTA naïve and MAIC, respectively, and 23.7% for GIMEMA-QW, ALCYONE, and PETHEMA/GEM05 pooled data for both comparisons (naïve, $p = .010$; MAIC, $p = .001$). Contrary to the CR rates, no significant differences in ORRs (CR + PR) were observed between the modified VMP schedule and the VISTA VMP regimen (Table 4). ORRs were 71.2% and 72.4% for VISTA naïve and MAIC, respectively, compared with 76.1% (naïve and MAIC) for the pooled GIMEMA-QW and ALCYONE data (Table 4). Using median (15%) and mean (13%) noninferiority margins, GIMEMA-QW and ALCYONE data were most likely noninferior to VISTA for ORR in the primary analysis for both naïve comparison and the MAIC, based on the rate differences. Similar results were observed with the sensitivity: for both the naïve comparison and the MAIC, there were no significant differences between VISTA (71.2% and 72.5%,



No. at risk						
VISTA VMP (unweighted)	344	161	1	0	0	0
Pooled modified VMP (primary analysis)	547	314	68	29	6	0
VISTA VMP (weighted)	263	127	0	0	0	0

Figure 1. Kaplan-Meier plots of PFS (primary analysis). Pooled ALCYONE, GIMEMA-QW, GIMEMA-QW + ALCYONE; Unweighted, naïve comparison; Weighted, MAIC. MAIC: modified-adjusted indirect comparison; PFS: progression-free survival; QW: once weekly; VMP: bortezomib-melphalan-prednisone.

Table 4. Efficacy outcomes in the primary and sensitivity analyses based on VISTA and modified VMP dosing schedules.

	Primary analysis		Sensitivity analysis	
Outcome (EBMT criteria)	VISTA	GIMEMA-QW + ALCYONE	VISTA	GIMEMA-QW + ALCYONE + PETHEMA/GEM05
Median PFS[a] (95% CI), months				
Naïve comparison	19.1 (17.8–21.6)	19.6 (18.8–21.0)	19.1 (17.8–21.6)	22.2 (20.2–24.1)
HR (95% CI)[b]		0.911 (0.756–1.097)		0.78 (0.65–0.937)
p value[c]		.326		.008
MAIC	20.7 (18.4–24.3)	19.6 (18.8–21.0)	20.7 (18.4–24.3)	22.2 (20.2–24.1)
HR (95% CI)[b]		0.991 (0.807–1.218)		0.848 (0.691–1.042)
p value[c]		.935		.117
CR, *n* (%)				
Naïve comparison	106 (31.5)	134 (24.6)	106 (31.5)	160 (23.7)
Rate difference (95% CI)		−6.82 (−12.96 to −0.68)		−7.72 (−13.62 to −1.81)
p value[d]		.029		.010
MAIC	90.9 (35.4)	134 (24.6)	87.9 (35.0)	160 (23.7)
Rate difference (95% CI)		−10.73 (−17.6 to −3.85)		−11.29 (−18.01 to −4.57)
p value[d]		.002		.001
ORR[e] (CR + PR), *n* (%)				
Naïve comparison	240 (71.2)	414 (76.1)	240 (71.2)	518 (76.9)
Rate difference (95% CI)		4.89 (−1.13 to 10.9)		5.64 (−0.15 to 11.43)
p value[d]		.113		.054
MAIC	185.9 (72.4)	414 (76.1)	181.7 (72.4)	518 (76.9)
Rate difference (95% CI)		3.75 (−2.79 to 10.29)		4.4 (−1.98 to 10.79)
p value[d]		.258		.196

CI: confidence interval; CR: complete response; EBMT: European Society for Blood and Marrow Transplantation; HR: hazard ratio; MAIC: matched-adjusted indirect comparison; NE: not estimable; ORR: overall response rate; PFS: progression-free survival; PR: partial response.
[a]The mean and median noninferiority margins for PFS were 1.314 and 1.300, respectively.
[b]Hazard ratio estimate is based on a Cox regression model unweighted in the case of the naïve comparison and weighted by individual weights in the MAIC.
[c]Score (log-rank) test.
[d]Two-sided *p* value based on Fisher's exact test.
[e]The mean/median noninferiority margins for ORR were 13% and 15%, respectively.

respectively) and GIMEMA-QW, ALCYONE, and PETHEMA/GEM05 pooled data (76.9% for both comparisons; Table 4). Using the same noninferiority margins as the primary analysis, GIMEMA-QW, ALCYONE, and PETHEMA/GEM05 pooled data were noninferior to VISTA for the naïve comparison and the MAIC.

Safety

AEs were examined across all 4 trials; however, not all trials collected outcomes equally so comparisons were limited. Incidences of peripheral neuropathy were significantly reduced with the modified VMP dosing schedule compared with the VISTA schedule for both the naïve comparison and the MAIC in the primary analysis (Table 5). Similar results were obtained for the sensitivity analysis (Table 5). Dose reductions due to peripheral neuropathy occurred in 17.4% of patients in the pooled GIMEMA-QW and ALCYONE studies compared with 19.1% and 19.8% for the naïve comparison and the MAIC, respectively, of VISTA.

For all other safety endpoints, in all analyses, the 95% CI of the rate difference crossed zero (Table 6), suggesting no statistical difference between VISTA VMP and modified VMP regimens. Data were not available from the GIMEMA study for treatment-related hematologic AEs; therefore, the primary analysis could not be performed for the key hematologic endpoints (Table 6).

Discussion

VMP is a well-established regimen for patients with NDMM who are transplant ineligible. However, substantial toxicity associated with the approved VMP dosing schedule led to dose reductions or premature discontinuation of therapy [9,10]. The treatment of patients with MM is continually evolving, and studies are being designed and conducted to evaluate different dosing regimens and drug combinations, with the goal of improving patient outcomes. Indirect comparison of results across studies can provide useful insights into the relative efficacy of various treatment options when direct head-to-head comparative trials do not exist. However, traditional methods of indirect comparison use meta-regression to adjust for cross-trial differences and typically require a common comparator [21]. An alternative approach, MAIC, compares absolute treatment effects while minimizing the risk of bias due to population differences and is preferred to naïve indirect comparisons [21].

In the present analysis, a modified VMP dosing schedule was investigated in 3 clinical trials, and the efficacy and safety of the modified regimens were indirectly compared to the original regimen using

Table 5. Summary of peripheral neuropathies by grade in the primary and sensitivity analyses based on VISTA and modified VMP dosing schedules.

	Primary analysis		Sensitivity analysis	
Outcome	VISTA	GIMEMA-QW + ALCYONE	VISTA	GIMEMA-QW + ALCYONE + PETHEMA/GEM05
Peripheral neuropathy, all grades, *n* (%)				
Naïve comparison	159 (46.8)	175 (32.1)	159 (46.8)	208 (30.8)
Rate difference (95% CI)		−14.65 (−21.25 to −8.06)		−15.95 (−22.3 to −9.6)
p value[a]		<.0001		<.0001
MAIC[b]	121.5 (46.7)	175 (32.1)	120 (47.2)	208 (30.8)
Rate difference (95% CI)		−14.63 (−21.85 to −7.4)		−16.43 (−23.49 to −9.37)
p value[a]		<.0001		<.0001
Peripheral neuropathy, grades 2–4, *n* (%)				
Naïve comparison	109 (32.1)	79 (14.5)	109 (32.1)	99 (14.7)
Rate difference (95% CI)		−17.56 (−23.34 to −11.79)		−17.39 (−23.03 to −11.76)
p value[a]		<.0001		<.0001
MAIC[b]	85.1 (32.7)	79 (14.5)	84.2 (33.2)	99 (14.7)
Rate difference (95% CI)		−18.24 (−24.66 to −11.81)		−18.51 (−24.89 to −12.13)
p value[a]		<.0001		<.0001
Peripheral neuropathy, grades 3 or 4, *n* (%)				
Naïve comparison	46 (13.5)	22 (4)	46 (13.5)	31 (4.6)
Rate difference (95% CI)		−9.49 (−13.49 to −5.5)		−8.94 (−12.9 to −4.97)
p value[a]		<.0001		<.0001
MAIC[b]	27.3 (10.5)	22 (4)	26.1 (10.3)	31 (4.6)
Rate difference (95% CI)		−6.49 (−10.57 to −2.41)		−5.68 (−9.74 to −1.63)
p value[a]		<.0001		.001

CI: confidence interval; MAIC: matched adjusted indirect comparison; QW: once weekly; VMP: bortezomib-melphalan-prednisone.
[a]Two-sided *p* value based on Fisher's exact test.
[b]Sample size of MAIC is weighted.

MAIC, as evaluated in the VISTA trial. By reducing the frequency of twice-weekly bortezomib dosing to only the first cycle of treatment [20] or using only QW bortezomib dosing [18,19], efficacy was maintained and the frequency of peripheral neuropathy was reduced. Efficacy results were similar across VISTA and the modified VMP trials for PFS and ORR, and showed noninferiority between the VMP regimens based on the HRs and response rate differences, respectively. CR rates were significantly higher in the VISTA trial, but these differences did not appear to translate into longer-term benefits for PFS. The primary MAIC analysis for PFS determined an HR of 0.991.

The median cumulative dose of bortezomib was similar across VISTA, ALCYONE, and GIMEMA-QW trials for all 9 cycles. In the PETHEMA/GEM05 trial, data were reported for 6 cycles, and the median cumulative dose of bortezomib was slightly lower than that of the other trials. The proportion of the planned bortezomib dose that was administered was lower in the VISTA trial compared with the other trials using the modified regimen. This finding is likely the result of fewer dose reductions of bortezomib in the GIMEMA and PETHEMA/GEM05 QW trials, whereas in VISTA, the median dose per cycle for bortezomib decreased gradually during twice-weekly administration in Cycles 1 to 4 but remained stable in the QW Cycles 5 to 9. Treatment discontinuations due to AEs in all cycles were similar between the VISTA VMP schedule and the pooled data from the modified VMP schedules. However, the incidence of peripheral neuropathy demonstrated a statistically significant reduction in modified VMP schedules as compared to the VISTA schedule. This effect was not associated with a significant difference in dose reductions or discontinuations due to peripheral neuropathy. The incidences of all deaths and key hematologic parameters were generally similar between all studies. VMP dosing schedules that employ primarily QW dosing, except for the first cycle, appear to be generally well tolerated. In addition, proactive management of AEs is critical to prolonging treatment for a chance at improved outcomes. This approach is particularly important for elderly patients who may have a compromised ability to tolerate antimyeloma therapy and demonstrate a high attrition rate after the first line of therapy [41].

The primary analysis pooled data from the GIMEMA-QW and ALCYONE trials. Data from the GIMEMA trial had been previously compared to the VISTA trial by Mateos et al. [10]; the ALCYONE trial was not available at that time. In addition to reducing the dose intensity of bortezomib, the ALCYONE trial evaluated the addition of daratumumab to the VMP regimen in untreated nontransplant patients with MM [20]. Results of a prespecified interim analysis of this randomized phase 3 trial reported similar median PFS between the control VMP arm (18.1 months) and that observed in the VISTA trial (18.3 months) [9,42].

Table 6. Summary of AEs leading to treatment (VMP) discontinuation and all deaths in the primary and sensitivity analyses and hematologic toxicities endpoints for the sensitivity analysis based on VISTA and Modified VMP dosing schedules.

	Primary analysis		Sensitivity analysis	
Outcome	VISTA	GIMEMA-QW + ALCYONE	VISTA	GIMEMA-QW + ALCYONE + PETHEMA/GEM05
Discontinuation due to AEs, all cycles, *n* (%)				
Naïve comparison	52 (15.3)	59 (10.8)	52 (15.3)	74 (11)
Rate difference (95% CI)		−4.47 (−9.1 to 0.16)		−4.33 (−8.82 to 0.16)
p value[a]		.060		.055
MAIC[b]	40.1 (15.4)	59 (10.8)	40.3 (15.9)	74 (11)
Rate difference (95% CI)		−4.62 (−9.73 to 0.49)		−4.92 (−10 to 0.16)
p value[a]		.067		.056
Discontinuation due to AEs, early cycles (Cycles 1–4), *n* (%)				
Naïve comparison	37 (10.9)	40 (7.3)	Early cycle data not available in the PETHEMA/GEM05 trial	
Rate difference (95% CI)		−3.54 (−7.51 to 0.43)		
p value[a]		.085		
MAIC[b]	27.5 (10.6)	40 (7.3)		
Rate difference (95% CI)		−3.25 (−7.59 to 1.08)		
p value[a]		.106		
Discontinuation due to peripheral neuropathy, *n* (%)				
Naïve comparison	11 (3.2)	15 (2.8)	11 (3.2)	22 (3.3)
Rate difference (95% CI)		−0.48 (−2.81 to 1.85)		0.02 (−2.29 to 2.33)
p value[a]		.6866		1.000
MAIC[b]	7.9 (3.1)	15 (2.8)	8.5 (3.3)	22 (3.3)
Rate difference (95% CI)		−0.3 (−2.81 to 2.2)		−0.09 (−2.67 to 2.5)
p value[a]		.823		1.000
Death during treatment, *n* (%)				
Naïve comparison	19 (5.6)	24 (4.4)	19 (5.6)	31 (4.6)
Rate difference (95% CI)		−1.18 (−4.17 to 1.8)		−1 (−3.9 to 1.91)
p value[a]		.426		.539
MAIC[b]	13 (5)	24 (4.4)	13.6 (5.3)	31 (4.6)
Rate difference (95% CI)		−0.6 (−3.76 to 2.56)		−0.75 (−3.93 to 2.44)
p value[a]		.721		.607

			Sensitivity analysis	
			VISTA	ALCYONE + PETHEMA/GEM05
Anemia, grade 3 or 4, *n* (%)				
Naïve comparison	–	–	64 (18.8)	85 (17.6)
Rate difference (95% CI)	–	–		−1.26 (−6.62 to 4.1)
p value[a]	–	–		.647
MAIC[b]	–	–	44.9 (16.4)	85 (17.6)
Rate difference (95% CI)	–	–		1.12 (−4.43 to 6.67)
p value[a]	–	–		.764
Neutropenia, grade 3 or 4, *n* (%)				
Naïve comparison	–	–	136 (40)	189 (39)
Rate difference (95% CI)	–	–		−0.95 (−7.73 to 5.83)
p value[a]	–	–		.828
MAIC[b]	–	–	115.2 (42.2)	189 (39)
Rate difference (95% CI)	–	–		−3.12 (−10.42 to 4.17)
p value[a]	–	–		.440
Thrombocytopenia, grade 3 or 4, *n* (%)				
Naïve comparison	–	–	130 (38.2)	169 (34.9)
Rate difference (95% CI)	–	–		−3.32 (−10.01 to 3.37)
p value[a]	–	–		.339
MAIC[b]	–	–	98.6 (36.1)	169 (34.9)
Rate difference (95% CI)	–	–		−1.19 (−8.3 to 5.92)
p value[a]	–	–		.752

AE: adverse event; CI: confidence interval; MAIC: matched-adjusted indirect comparison; QW: once weekly; VMP: bortezomib-melphalan-prednisone.
[a]Two-sided *p* value based on Fisher's exact test.
[b]Sample size of MAIC is weighted.

In addition, the trial identified a 50% lower risk of disease progression or death with daratumumab-VMP compared with VMP alone (HR, 0.50; 95% CI, 0.38–0.65; $p < .001$) [20]. The addition of daratumumab was associated with a lower rate of peripheral neuropathy, but higher rates of infusion-related reactions and infections.

This retrospective analysis of data from three clinical trials has several limitations. One limitation common to all clinical trial data is the difficulty in interpreting results from a rigorously controlled trial in the context of clinical practice. Care should also be taken when comparing data from different trials and, for this reason, this MAIC provides important results for the

clinician. Real-world evidence of outcomes with VMP are relatively lacking and have not investigated different VMP schedules [43–45]. Therefore, further investigation is warranted to build on the novel results of this present analysis. A limitation of this analysis was the lack of availability of individual patient data from some of the clinical trials. In addition, the MAIC analysis could not be adjusted for unreported or unobserved confounding factors. Weighting reduces the ESS and subsequently negatively affects the precision of the estimate. The methodology used to reconstruct individual patient data for time-to-event variables was based on the assumption of equal time censoring. Due to the retrospective aspect, the noninferiority margin was not prespecified based on clinical judgment; therefore, the analysis was not powered accordingly. Due to the retrospective nature of the analysis performed, the 95% CI of the noninferiority analysis should be used as a reference and not as a definitive rule to determine whether the less intensive VMP regimen is noninferior/inferior to the VISTA VMP regimen. Despite these limitations, the MAIC method is recommended for health technology assessment by the NICE in cases where there is a lack of connected randomized evidence or when single-arm studies are involved [28]. Importantly, the role of maintenance therapy after response to VMP in nontransplant patients was not assessed; this along with differences in the route of administration of bortezomib across trials (subcutaneous in ALCYONE and intravenous in all other trials in this comparison) may have influenced the results.

The findings of both MAIC and naïve comparisons support the use of a modified VMP dosing schedule for patients with NDMM who are transplant ineligible. As naïve indirect comparisons are prone to bias due to patient heterogeneity between studies, a MAIC can provide useful insights for clinicians and reimbursement decision-makers on the relative efficacy and safety of different treatments when no head-to-head trial has been conducted. This MAIC analysis demonstrates similar efficacy of modified VMP with VISTA VMP and a potential reduction in rates of peripheral neuropathy. Proactive management of AEs is critical for prolonging treatment for a chance at improved outcomes, and this is particularly important for elderly patients who may have a compromised ability to tolerate any antimyeloma therapy and demonstrate a high attrition rate after the first line of therapy [41]. It is critical to minimize toxicity without a loss of efficacy to ensure continued treatment. Taken together, these findings demonstrate a favorable benefit/risk profile of a modified VMP regimen in a clinical trial setting and support the use of a modified VMP dosing schedule for patients with NDMM who are transplant ineligible.

Author contributions

MAD and JH contributed to conception of study design, data acquisition and analysis/interpretation; MH, BH, and AL contributed to conception of study design and data analysis/interpretation; HG contributed to data acquisition and analysis/interpretation; WD contributed to conception of study design and data acquisition; PS contributed to data acquisition; JSM contributed to conception of study design; PH and M-VM contributed to data analysis/interpretation. All authors drafted and reviewed the manuscript, approved the final version, decided to publish this report, and vouch for data accuracy and completeness.

Disclosure statement

M-VM served as a consultant and on the board of directors or advisory committees for Amgen, GlaxoSmithKline, Celgene, Janssen, Takeda, and AbbVie; and received honoraria from Amgen, Celgene, Janssen, and Takeda. JS-M received honoraria from Janssen, Celgene, Amgen, Bristol-Myers Squibb, Novartis, Sanofi, and Roche. HG served as a consultant for Adaptive Biotechnology, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Sanofi, and Takeda; received research funding from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Sanofi, Takeda, Chugai, Mundipharma, and Novartis; and received honoraria from Bristol-Myers Squibb, Celgene, Janssen, Chugai, Novartis, and ArtTempi. PS received honoraria and research funding from Amgen, Celgene, Janssen, Karyopharm, and Bristol-Myers Squibb. MAD received honoraria from Janssen, Celgene, Takeda, Amgen, and Bristol-Myers Squibb. BH received equity ownership and research funding from and is an employee of Ingress Health Nederland BV. MH is an employee of Ingress Health. WD, PH, AL, and JH are employees of Janssen.

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ORCID

Maria-Victoria Mateos http://orcid.org/0000-0003-2390-1218
Jesus San-Miguel http://orcid.org/0000-0002-9183-4857
Hartmut Goldschmidt http://orcid.org/0000-0003-0961-0035
Pieter Sonneveld http://orcid.org/0000-0002-0808-2237
Meletios A. Dimopoulos http://orcid.org/0000-0001-8990-3254
Bart Heeg http://orcid.org/0000-0002-9226-3232

Mahmoud Hashim http://orcid.org/0000-0002-5775-9590
William Deraedt http://orcid.org/0000-0003-1414-2387
Peter Hu http://orcid.org/0000-0002-4061-8484
Annette Lam http://orcid.org/0000-0003-2037-3464
Jianming He http://orcid.org/0000-0002-5015-3713

Data availability statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) project site at http://yoda.yale.edu.

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