Original Study

Comparative Efficacy of Bortezomib, Melphalan, and Prednisone (VMP) With or Without Daratumumab Versus VMP Alone in the Treatment of Newly Diagnosed Multiple Myeloma: Propensity Score Matching of ALCYONE and VISTA Phase III Studies

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Abstract

A propensity score-matched analysis compared bortezomib, melphalan, and prednisolone (VMP) in the ALCYONE study (± daratumumab [D]) with VMP in the VISTA study because no direct comparisons are available. Results indicated a lower intensity VMP regimen such as in ALCYONE has a favorable benefit/risk profile compared with the VISTA VMP schedule and D-VMP significantly improves efficacy versus VISTA VMP.

Introduction: Bortezomib, melphalan, and prednisone (VMP) is the standard of care for transplant-ineligible newly diagnosed multiple myeloma. The phase III VISTA trial established the bortezomib dosing schedule for VMP. To mitigate bortezomib-associated toxicity, the phase III ALCYONE study of daratumumab plus VMP (D-VMP) versus VMP used modified bortezomib dosing. D-VMP demonstrated improved progression-free survival and overall response rate. Propensity score matching enables indirect comparisons by controlling for differences in baseline covariates. **Patients and Methods:** The efficacy and safety of both arms of ALCYONE were compared with VISTA VMP using propensity score matching. ALCYONE D-VMP and VMP patients were matched on selected baseline characteristics to VISTA VMP patients, reducing or eliminating systematic differences between treatment groups. **Results:** After matching, median progression-free survival and overall response rate were comparable for ALCYONE VMP and VISTA VMP, and were significantly improved with ALCYONE D-VMP versus VISTA VMP. Rates of grade 3/4 peripheral sensory neuropathy were significantly lower for both arms of ALCYONE versus VISTA VMP, with or without matching. **Conclusion:** This propensity score matching analysis demonstrates significant improvements in efficacy with ALCYONE D-VMP versus VISTA VMP and a significantly lower incidence of peripheral sensory neuropathy in both arms of ALCYONE versus VISTA VMP, although safety improvements may be due to different bortezomib administration routes (ALCYONE, subcutaneous; VISTA, intravenous).

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Introduction

In Europe and the United States, many patients with newly diagnosed multiple myeloma (NDMM) receive a bortezomib-containing regimen.[1,2] Despite the efficacy of frontline bortezomib-based therapy, therapeutic options are needed for elderly or frail patients and those who have comorbidities rendering them ineligible for autologous stem cell transplantation.[3]

Daratumumab is a human IgGκ CD38-targeting monoclonal antibody with a direct[4-7] and immunomodulatory mechanism of action.[8-10] Daratumumab is approved in many countries as monotherapy for relapsed/refractory MM or in combination with standard-of-care regimens for relapsed/refractory MM or transplant-ineligible NDMM. Recently, based on results of the CASSIOPEIA study, the US Food and Drug Administration approved daratumumab in combination with bortezomib, thalidomide, and dexamethasone for transplant-eligible NDMM.[11]

The phase III VISTA study established the standard bortezomib/melphalan/prednisone (VMP) dosing schedule of twice-weekly (four 6-week cycles), followed by once-weekly (five 6-week cycles).[12,13] Subsequent trials, including GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto)[14] and PETHEMA/GEM05 (Programa Español de Tratamientos en Hematología)[15] investigated less intensive, modified VMP dosing schedules[16] to improve tolerability without compromising efficacy. GIMEMA used weekly dosing (nine 5-week cycles), and PETHEMA/GEM05 used bortezomib twice-weekly (one 6-week cycle), followed by once-weekly (five 5-week cycles). A subcutaneous formulation of bortezomib was developed and approved in 2012.[17] Together, these alterations resulted in VMP regimens that decreased bortezomib-associated toxicity without sacrificing efficacy.[14,15,17]

ALCYONE is an ongoing randomized, controlled, multicenter, open-label, phase III study in transplant-ineligible NDMM (ClinicalTrials.gov Identifier: NCT02195479). This study compares daratumumab plus a modified VMP schedule (D-VMP), different from those used in GIMEMA and PETHEMA/GEM05, with a modified VMP schedule alone.[18] The less intensive VMP schedule in ALCYONE reduced the twice-weekly dosing of bortezomib to once-weekly after the first cycle.[18] With a median follow-up of 16.5 months, D-VMP decreased the risk of disease progression or death by 50% versus VMP with a tolerable safety profile, leading to the approval of D-VMP in many countries.[18,19] With additional follow-up (median of 27.8 months), D-VMP continued to demonstrate significantly improved efficacy versus VMP.[20]

In the absence of head-to-head clinical trials, it remains unclear whether the ALCYONE modified VMP dosing provides a similar efficacy and/or superior clinical benefit to that of VISTA VMP.[16] Propensity score matching (PSM) enables an indirect comparison between treatment groups of different studies by controlling for differences in baseline covariates.[21,22] Here, we report the efficacy and safety of ALCYONE D-VMP or VMP versus VISTA VMP[16] using a PSM analysis conducted based on comparable follow-up times using the 2008 data cut for VISTA[23] and June 2018 data cut for ALCYONE[20] (median of 27.8 months vs. median of 25.9 months, respectively).

Materials and Methods

Study Design and Treatment

ALCYONE (NCT02195479) is a randomized phase III study of D-VMP versus VMP in patients with NDMM who are transplant ineligible.[18] Patients were randomized 1:1 to receive up to nine 6-week cycles of VMP (bortezomib 1.3 mg/m^2 subcutaneously twice-weekly during cycle 1 and once-weekly during cycles 2-9; melphalan 9 mg/m^2 orally on days 1-4 of each cycle; and prednisone 60 mg/m^2 orally on days 1-4 of each cycle), with or without daratumumab 16 mg/kg intravenously every week in cycle 1, every 3 weeks for cycles 2-9, and every 4 weeks for cycles 10 and onward (post-VMP treatment phase) until disease progression or unacceptable toxicity.[18] Bortezomib was administered subcutaneously based on findings from the phase III randomized noninferiority study that demonstrated comparable efficacy but an improved safety profile observed with subcutaneous versus intravenous bortezomib administration.[17]

VISTA was a phase III study of melphalan and prednisone with or without bortezomib in patients with NDMM who were transplant ineligible.[13] In VISTA, patients in the VMP arm received up to nine 6-week cycles of VMP (bortezomib 1.3 mg/m^2 intravenously twice-weekly during cycles 1-4 and weekly during cycles 5-9; melphalan 9 mg/m^2 orally on days 1-4 of cycles 1-9; and prednisone 60 mg/m^2 orally on days 1-4 of cycles 1-9).

Efficacy Endpoints

The primary efficacy endpoint of ALCYONE was progression-free survival (PFS), whereas the primary efficacy endpoint of VISTA was time to progression. Disease progression for ALCYONE was determined using the International Myeloma Working Group (IMWG) criteria.[24,25] Disease progression for VISTA VMP was originally based on European Society for Blood and Marrow Transplantation (EBMT) criteria[26]; a post hoc assessment based on IMWG criteria was published, using an updated dataset with longer follow-up.[27] In this analysis, PFS based on EBMT criteria for VISTA was used as the base-case as it has a similar follow-up period compared with ALCYONE. For a sensitivity analysis, disease progression assessment of patients treated with VISTA VMP was redefined based on International Uniform Response Criteria, later termed the IMWG criteria.[24,25] For consistency with ALCYONE, the PFS of VISTA was censored at subsequent therapy.

PSM

Age, gender, renal function (creatinine clearance $\leq$60 mL/min and >60 mL/min), International Staging System disease stage (I, II, and III), heavy chain isotype (IgG, non-IgG), and Eastern Cooperative Oncology Group (ECOG) performance score (0, $\geq$1) were variables identified for both matching and adjusting based on clinical judgment. Karnofsky Performance Status scores recorded in VISTA were converted to ECOG performance scores. The proportion of patients for whom cytogenetic testing was performed was low in VISTA and would have substantially decreased the number of patients available for matching; therefore, this variable was not included for matching.

Table 1 Key Baseline Demographics and Characteristics of ALCYONE VMP and VISTA VMP-Treated Patients

	Original Sample				Matched Sample			
	VISTA VMP (n = 344)	ALCYONE VMP (n = 356)	Standardized Difference	Variance Ratio	VISTA VMP (n = 278)	ALCYONE VMP (n = 278)	Standardized Difference	Variance Ratio
Age, y	72.2 ± 5.7	71.5 ± 5.8	0.121	1.05	71.8 ± 5.3	71.7 ± 6.0	0.027	1.278
ECOG								
1	179 (52.0)	173 (48.6)	0.069	1.001	148 (53.2)	164 (59.0)	0.116	0.972
≥2	120 (34.9)	84 (23.6)	0.250	0.794	85 (30.6)	84 (30.2)	0.008	0.993
Male	175 (50.9)	167 (46.9)	0.079	0.996	134 (48.2)	134 (48.2)	0	1
ISS								
I	64 (18.6)	67 (18.8)	0.0006	1.009	49 (17.6)	51 (18.3)	0.019	1.032
II	161 (46.8)	160 (44.9)	0.0374	0.994	126 (45.3)	128 (46.0)	0.014	1.003
IgG	214 (62.2)	218 (61.2)	0.020	1.010	173 (62.2)	171 (61.5)	0.015	1.007
Creatinine clearance								
≤60 mL/min	185 (53.8)	145 (40.7)	0.264	0.971	148 (53.2)	130 (46.8)	0.130	1

Values are mean ± SD or number (%) unless otherwise indicated.
Abbreviation: ISS = International Staging System.

Confounding distorts the relationship between exposure and outcome, leading to erroneous conclusions, highlighting the need to control for confounding for accuracy. Confounding can be controlled by randomization, restriction, and matching of the dependent variables.[28] Both matching and adjusting are valid methods in this post hoc comparison between ALCYONE and VISTA. We report the results by naïve and matched comparisons, and by unadjusted and adjusted models.

Propensity scores were estimated by logistic regression, in which the treatment group was regressed on matching variables. Data from the 2 groups were matched on the logit of the propensity score. A greedy algorithm was used, in which once a match was made, the match was not reconsidered.[29] Standardized differences and variance ratios were determined to assess the similarity of baseline covariates between treatment groups before and after matching.[21]

Statistical Analyses

Differences between groups using log-rank tests before and after matching for PFS and time to progression were compared. Hazard ratios (HRs) of time to events were also estimated with the use of a Cox proportional hazards model for treatment effect with and without adjusting matching variables before and after matching. *P* values for HRs and Kaplan-Meier curves were based on the Wald test and log-rank test, respectively. Response rates and adverse event (AE) rates were analyzed on the basis of the Cochran-Mantel-Haenszel χ^2 test.

Results

Patient Characteristics

A total of 706 patients in ALCYONE (350 in D-VMP; 356 in VMP) and 682 patients in VISTA (344 in VMP; 338 in melphalan and prednisone) were randomized in the respective phase III studies for patients with NDMM who are transplant ineligible. Among patients in the ALCYONE VMP and VISTA VMP groups, a total of 278 patients were matched by age, gender, International Staging System stage, type of MM, ECOG performance score, and creatinine clearance. A naïve, unmatched comparison of baseline characteristics between the ALCYONE VMP and VISTA VMP arms identified differences in age, ECOG performance status, and creatinine clearance, which were substantially decreased or eliminated after matching (Table 1). Standardized differences in the original sample ranged from 0.006 to 0.264. After matching, the greatest standardized difference was 0.13, with the variance ratios closer to 1 in several cases. Among patients in the ALCYONE D-VMP and VISTA VMP groups, a total of 281 patients were matched. Statistically significant ($P < .05$) differences in baseline characteristics were observed for age, ECOG performance status, and creatinine clearance (Table 2). Standardized differences in the original sample ranged between 0.001 and 0.220. After matching, the largest standardized difference was 0.029, and the variance ratio was closer to 1.

Efficacy Comparisons

PFS: ALCYONE VMP Versus VISTA VMP. Because disease progression in VISTA was originally defined based on EBMT criteria,[26] the PFS analyses in this PSM were conducted based on EBMT criteria. At a median follow-up of 27.4 months, the median PFS for the ALCYONE VMP arm was 19.1 months (95% CI, 17.9-20.4 months) versus 19.1 months (95% CI, 17.7-21.4 months) for the VISTA VMP arm.[13,20] Based on naïve comparisons, the unadjusted PFS HR of ALCYONE VMP versus VISTA VMP was 0.99 (95% CI, 0.81-1.21; $P = .9478$), when EBMT criteria were used for VISTA VMP (Figure 1A). The adjusted PFS HR was 1.02 (95% CI, 0.83-1.26; $P = .8506$). After matching, median PFS for ALCYONE VMP was 18.9 months (95% CI, 17.1-20.1 months) versus 18.7 months (95% CI, 16.6-20.7 months) for VISTA VMP (Figure 1B), leading to an unadjusted HR of 0.95 (95% CI, 0.76-1.18; $P = .6409$) based on EBMT criteria. The adjusted HR for the PFS comparison based on EBMT criteria was 0.94 (95% CI, 0.75-1.17; $P = .5704$).

Table 2 Key Baseline Demographics and Characteristics of ALCYONE D-VMP and VISTA VMP-Treated Patients

	Original Sample				Matched Sample			
	VISTA VMP (n = 344)	D-VMP (n = 350)	Standardized Difference	Variance Ratio	VISTA VMP (n = 281)	D-VMP (n = 281)	Standardized Difference	Variance Ratio
Age, y	72.2 ± 5.7	71.3 ± 6.7	0.156	1.378	71.9 ± 5.6	72.1 ± 6.2	0.028	1.249
ECOG								
1	179 (52.0)	182 (52.0)	0.001	1.000	151 (53.7)	155 (55.2)	0.029	0.995
≥2	120 (34.9)	90 (25.7)	0.201	0.841	86 (30.6)	83 (29.5)	0.023	0.98
Male	175 (50.9)	160 (45.7)	0.103	0.993	138 (49.1)	138 (49.1)	0	1
ISS								
I	64 (18.6)	69 (19.7)	0.028	1.045	53 (18.9)	56 (19.9)	0.027	1.043
II	161 (46.8)	139 (39.7)	0.143	0.962	125 (44.5)	121 (43.1)	0.029	0.993
IgG	214 (62.2)	207 (59.1)	0.063	1.028	167 (59.4)	171 (60.9)	0.029	0.988
Creatinine clearance								
≤60 mL/min	185 (53.8)	150 (42.9)	0.220	0.985	135 (48.0)	135 (48.0)	0	1

Values are mean ± SD or number (%) unless otherwise indicated.
Abbreviation: ISS = International Staging System.

In a sensitivity analysis based on naïve comparisons using IMWG criteria to define progression, the median PFS for VISTA VMP was 20.7 months (95% CI, 17.2-24.7 months), leading to an unadjusted HR of 1.04 (95% CI, 0.82-1.31; $P = .7446$). The adjusted HR of PFS comparison based on IMWG criteria was 1.06 (95% CI, 0.83-1.36; $P = .6213$). After matching, the median PFS for ALCYONE VMP was 18.9 months (95% CI, 17.1-20.1 months) versus 20.0 months (95% CI, 16.6-23.1 months) for VISTA VMP based on EMBT criteria. The unadjusted and adjusted HRs comparing ALCYONE and VISTA VMP based on IMWG criteria were 1.00 (95% CI, 0.77-1.29; $P = .9853$) and 0.97 (95% CI, 0.75-1.26, $P = .8347$), respectively.

Overall Response Rate: ALCYONE VMP Versus VISTA VMP. The unmatched overall response rate (ORR) was 73.9% for ALCYONE VMP versus 71.2% for VISTA VMP based on EBMT criteria ($P = .4331$; Table 3). Responses of complete response or better were achieved in 25.3% and 31.5% of patients who received ALCYONE VMP versus VISTA VMP, respectively ($P = .0715$). After matching, the ORR was 72.7% for ALCYONE VMP versus 71.4% for VISTA VMP, based on EBMT criteria ($P = .7473$), with lower responses of complete response or better achieved with ALCYONE VMP versus VISTA VMP (24.1% vs. 30.4%; $P = .0969$; Table 3). Table 3 also shows responses based on a sensitivity analysis using IMWG criteria for VISTA VMP.

PFS: ALCYONE D-VMP Versus VISTA VMP. Based on the updated ALCYONE analysis, at a median follow-up of 27.8 months, median PFS for ALCYONE D-VMP was not reached versus 19.1 months (95% CI, 17.7-21.4 months; $P < .0001$) for VISTA VMP (Figure 2A). In the naïve comparison, the unadjusted PFS HR of D-VMP versus VISTA VMP was 0.46 (95% CI, 0.36-0.58; $P < .0001$). The adjusted HR of PFS comparison for D-VMP versus VISTA VMP was 0.47 (95% CI, 0.37-0.60; $P < .0001$).

In a sensitivity analysis based on IMWG criteria for VISTA, the median PFS of the VMP treatment group in VISTA was 20.7 months (95% CI, 17.2-24.7 months; $P < .0001$). Based on naïve comparisons, the unadjusted PFS HR of D-VMP versus VISTA VMP was 0.52 (95% CI, 0.40-0.68; $P < .0001$) and the adjusted HR for PFS was 0.53 (95% CI, 0.40-0.70; $P < .0001$) based on IMWG criteria.

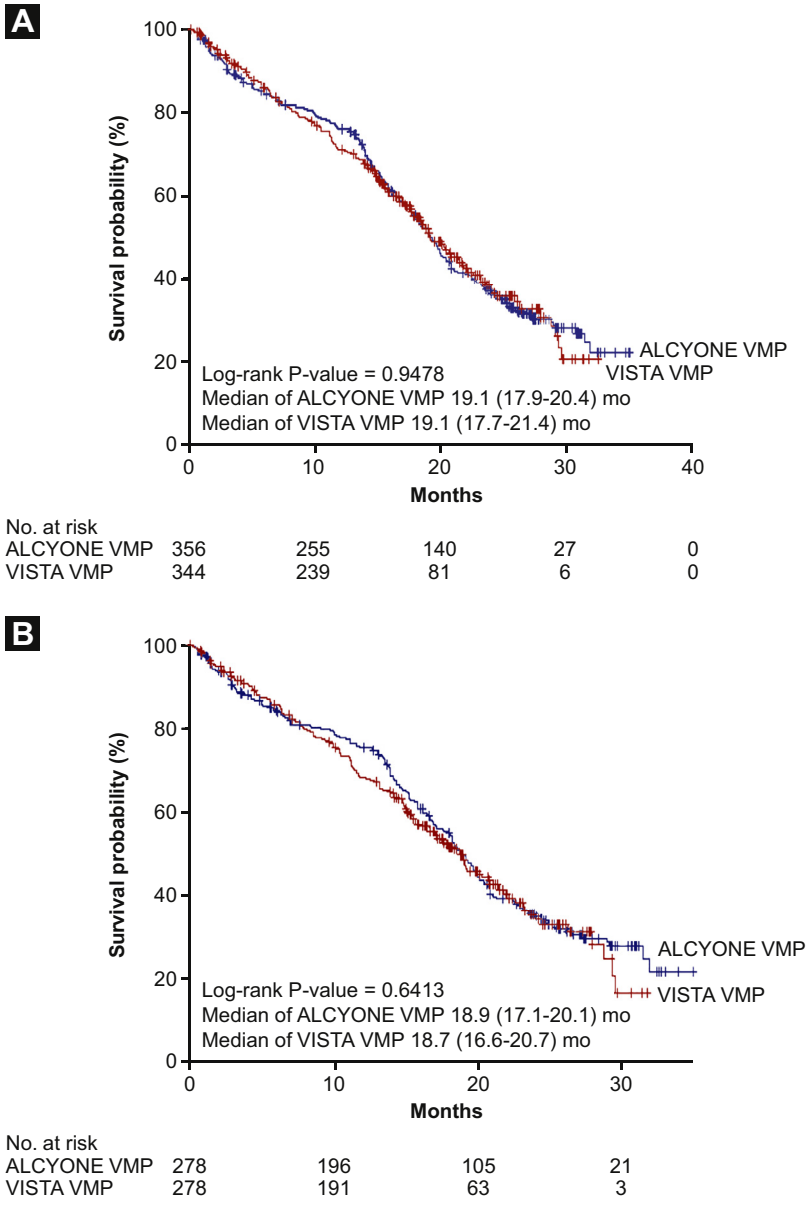
After matching, median PFS for D-VMP was not reached, compared with 19.0 months (95% CI, 17.5-21.4 months) for VISTA VMP based on EMBT criteria, leading to an unadjusted HR of 0.45 (95% CI, 0.35-0.59; $P < .0001$; Figure 2B) and an adjusted HR of 0.43 (95% CI, 0.33-0.56; $P < .0001$). The median PFS for VISTA VMP based on IMWG criteria was 20.6 months (95% CI, 16.7-not estimable), leading to an unadjusted HR of 0.50 for D-VMP versus VISTA VMP (95% CI, 0.37-0.67; $P < .0001$) and an adjusted HR of 0.47 (95% CI, 0.35-0.64; $P < .0001$).

ORR: ALCYONE D-VMP Versus VISTA VMP. The unmatched ORR was 90.9% for D-VMP versus 71.2% for VISTA VMP based on EBMT criteria for the VISTA study ($P < .0001$; Table 4). A complete response or better was achieved in 45.1% and 32.9% of patients who received D-VMP versus VISTA VMP, respectively ($P = .0002$). After matching, the ORR was 90.8% for D-VMP versus 71.2% for VISTA VMP based on EBMT criteria ($P < .0001$), with responses of complete response or better remaining higher with D-VMP versus VISTA VMP (44.5% vs. 33.2%; $P = .0065$; Table 4). Responses based on a sensitivity analysis using IMWG criteria are also presented in Table 4.

Safety Comparison

Safety: ALCYONE VMP Versus VISTA VMP. The rate of grade 3/4 peripheral sensory neuropathy was significantly lower with ALCYONE VMP versus VISTA VMP with or without matching ($P < .05$; Table 5). Rates of grade 3/4 hematologic AEs (including anemia, neutropenia, and thrombocytopenia) and grade 3/4 infections were

Figure 1 PFS of ALCYONE VMP Versus VISTA VMP Based on Naïve Comparisons (A) or After Matching (B)



either comparable or lower with ALCYONE VMP versus VISTA VMP, but were not statistically significant (Table 5). Grade 3/4 diarrhea, pyrexia, and nausea were significantly lower with ALCYONE VMP versus VISTA VMP before and after matching (Table 5). Additionally, the incidence of grade 3/4 pneumonia was significantly lower with ALCYONE VMP versus VISTA VMP after matching. A caveat to these safety comparisons is that these AEs were not adjusted for exposure; however, the mean ± SD cumulative dose of bortezomib was similar with ALCYONE VMP and VISTA VMP before (37.5 ± 15.2 mg/m^2 vs. 37.6 ± 20.6 mg/m^2) and after matching (37.4 ± 15.2 mg/m^2 vs. 38.2 ± 20.5 mg/m^2). The median cumulative dose was also similar between groups before (42.2 mg/m^2 [interquartile range {IQR}, 18.5-50.6 mg/m^2] vs. 39.0 mg/m^2 [IQR, 18.5-56.5 mg/m^2]) and after matching (42.5 mg/m^2 [IQR, 27.0-50.6 mg/m^2] vs. 40.2 mg/m^2 [IQR, 19.0-56.8 mg/m^2]).

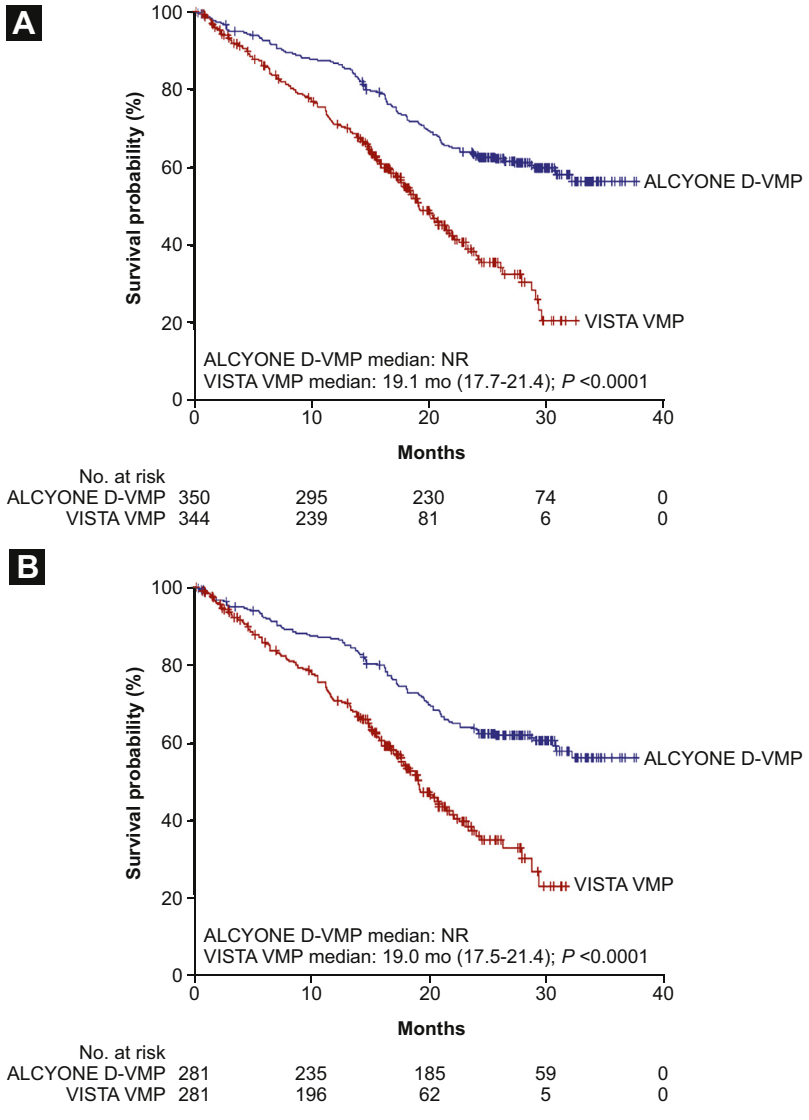
ALCYONE D-VMP Versus VISTA VMP. The rate of all grade 3/4 peripheral sensory neuropathy was also significantly lower with D-VMP versus VISTA VMP with or without matching ($P < .0001$; Table 6). Rates of grade 3/4 hematologic AEs (including anemia, neutropenia, and thrombocytopenia) and grade 3/4 infections were either comparable or lower with D-VMP compared with VISTA VMP, but were not statistically significant (Table 6). Grade 3/4 nausea was significantly lower with D-VMP versus VISTA VMP before and after matching (Table 6). Similar to the safety comparisons of ALCYONE VMP with VISTA VMP, the comparisons of

Table 3 Response Rates in Unmatched and Matched ALCYONE VMP and VISTA VMP-Treated Patients

	Unmatched					Matched				
	ALCYONE VMP (IMWG) (n = 356)	VISTA VMP (EBMT) (n = 337)	*P* Value	VISTA VMP (IMWG) (n = 337)	*P* Value	ALCYONE VMP (IMWG) (n = 278)	VISTA VMP (EBMT) (n = 273)	*P* Value	VISTA VMP (IMWG) (n = 273)	*P* Value
ORR	263 (73.9)	240 (71.2)	.4331	251 (74.5)	.9689	202 (72.7)	195 (71.4)	.7473	204 (74.7)	.5827
≥CR	90 (25.3)	106 (31.5)	.0715	111 (32.9)	.0265	67 (24.1)	83 (30.4)	.0969	89 (32.6)	.0269
PR	173 (48.6)	134 (39.8)	—	140 (41.5)	—	135 (48.6)	112 (41)	—	115 (42.1)	—
MR/SD	76 (21.4)	90 (26.7)	—	79 (23.4)	—	64 (23.0)	72 (26.4)	—	63 (23.1)	—
PD	2 (0.6)	3 (0.9)	—	3 (0.9)	—	1 (0.4)	3 (1.1)	—	3 (1.1)	—
NE	15 (4.2)	4 (1.2)	—	4 (1.2)	—	11 (4.0)	3 (1.1)	—	3 (1.1)	—

Disease progression assessment of ALCYONE was based on the IMWG criteria and disease progression assessment of VISTA was based on either the IMWG or EBMT criteria.
Values are number (%) unless otherwise indicated.
Abbreviations: ≥CR = complete response or better; MR = minimal response; NE = not estimable; PD = progressive disease; PR = partial response; SD = stable disease.

Figure 2 PFS of ALCYONE D-VMP Versus VISTA VMP Based on Naïve Comparisons (A) or After Matching (B)



Abbreviation: NR = not reached.

Table 4 Response Rates in Unmatched and Matched ALCYONE D-VMP and VISTA VMP-Treated Patients

	Unmatched					Matched				
	D-VMP (n = 350)	VISTA (EBMT) VMP (n = 337)	*P* Value	VISTA (IMWG) VMP (n = 337)	*P* Value	D-VMP (n = 281)	VISTA (EBMT) VMP (n = 274)	*P* Value	VISTA (IMWG) VMP (n = 274)	*P* Value
ORR	318 (90.9)	240 (71.2)	<.0001	251 (74.5)	<.0001	255 (90.8)	195 (71.2)	<.0001	204 (74.5)	<.0001
≥CR	158 (45.1)	106 (31.5)	.0002	111 (32.9)	.0011	125 (44.5)	91 (33.2)	.0065	94 (34.3)	.0143
PR/VGPR	160 (45.7)	134 (39.8)		140 (41.5)		130 (46.3)	104 (38.0)		110 (40.2)	
MR/SD	20 (5.7)	90 (26.7)		79 (23.4)		15 (5.3)	74 (27.0)		65 (23.7)	
PD	0.0	3 (0.9)		3 (0.9)		0.0	1 (0.4)		1 (0.4)	
NE	12 (3.4)	4 (1.2)		4 (1.2)		11 (3.9)	4 (1.5)		4 (1.5)	

Disease progression assessment of VISTA was based on the IMWG criteria.
Values are number (%) unless otherwise indicated.
Abbreviations: ≥CR = complete response or better; MR = minimal response; NE = not estimable; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response.

D-VMP versus VISTA VMP AEs were not adjusted for exposure. The mean ± SD cumulative dose of bortezomib was slightly higher with D-VMP than with VISTA VMP before (41.6 ± 13.1 mg/m^2 vs. 37.6 ± 20.6 mg/m^2) and after matching (41.1 ± 13.7 mg/m^2 vs. 37.9 ± 20.9 mg/m^2). Likewise, the median cumulative dose was slightly higher with D-VMP before (47.1 mg/m^2 [IQR, 37.2-51.1 mg/m^2] vs. 39.0 mg/m^2 [IQR, 18.5-56.5 mg/m^2]) and after matching (46.5 mg/m^2 [IQR, 35.9-51.1 mg/m^2] vs. 39.1 mg/m^2 [IQR, 18.4-57.7 mg/m^2]).

Discussion

In comparisons of VMP between the phase III studies ALCYONE and VISTA, imbalances in age, ECOG performance status, and creatinine clearance were observed. Regardless of matching baseline patient characteristics, our findings suggest that the modified VMP regimen in ALCYONE demonstrated comparable PFS results to the VMP dosing in VISTA, based on both IMWG and EBMT criteria. Additionally, ORRs of ALCYONE VMP were similar to ORRs of VISTA VMP, regardless of matching. Finally, in both matched and unmatched analyses, the rate of all-grade and grade 3/4 peripheral sensory neuropathy was significantly lower with ALCYONE VMP versus VISTA VMP. Although the safety comparisons of these AEs were not adjusted for exposure, it is worth noting that the comparable (or higher) cumulative dose of bortezomib in ALCYONE VMP and D-VMP compared with VISTA VMP was not associated with increased rates of sensory neuropathy.

When comparing the baseline characteristics of patients treated with ALCYONE D-VMP and VISTA VMP, statistically significant differences were observed in age, ECOG performance status, and creatinine clearance, which may have impacted the outcomes of patients enrolled in these studies. However, our findings suggest D-VMP had (1) significantly longer PFS based on either EBMT or IMWG criteria (unadjusted PFS HR for D-VMP vs. VISTA VMP of 0.45 after matching was comparable to the PFS HR of 0.50 reported for the primary analysis of ALCYONE[18] and 0.43 for the updated analysis[20]; (2) a significantly higher ORR and complete response; and (3) a significantly lower rate of grade 3/4 peripheral neuropathy and other AEs such as diarrhea and nausea, regardless of matching patient characteristics, versus VISTA VMP.

A comparison of outcomes for patients treated with different VMP dosing schedules in PETHEMA/GEM05 and VISTA using PSM revealed similar findings to those observed in the current comparison of D-VMP and VISTA VMP, showing that a lower intensity VMP schedule used in PETHEMA/GEM05 was associated with significantly longer PFS compared with VISTA VMP.[22] Unlike in ALCYONE, patients in PETHEMA/GEM05 received bortezomib-based maintenance treatment after 6 cycles of VMP, but similarly provide additional evidence supporting the use of lower intensity VMP dosing for patients with NDMM who are transplant ineligible.

Although improvements in clinical practice have taken place since the VISTA study, we consider the NDMM patient population of VISTA to be generally comparable to more recent studies. Although this PSM analysis provides important comparative data between both arms of ALCYONE (VMP and D-VMP) and VISTA VMP, several limitations exist. Information regarding cytogenetic risk was missing for more than one-half of patients enrolled in VISTA; therefore, matching patients by cytogenetic risk was not feasible without substantially decreasing the number of patients available for matching. Additionally, although several baseline characteristics were accounted for in the matching process, one cannot exclude residual confounding for other patient characteristics not included in the matching process. Although PFS for VISTA VMP was redefined to censor by subsequent therapy for consistency with ALCYONE, the results are slightly different than values reported in the corresponding primary analysis.[13] Nevertheless, comparable data from an updated data cut (based on IMWG criteria) were subsequently published for VISTA, although the study did not censor for subsequent therapy.[27]

Besides differences in the bortezomib dosing schedules used, other differences between these studies constitute a limitation of our analysis and must be noted. The subcutaneous administration of bortezomib demonstrated an improved safety profile versus intravenous administration in a phase III noninferiority study[17]; therefore, the difference in bortezomib administration routes in ALCYONE (subcutaneous) versus VISTA (intravenous) may be a contributing factor to the improved safety profile observed in ALCYONE. Based on the current analysis, it is not possible to determine which factor (dosing schedule, route of administration, or a combination thereof) resulted in the lower toxicity in ALCYONE

Table 5 All-Grade and Grade 3/4 TEAEs of Interest in Unmatched and Matched ALCYONE VMP and VISTA VMP-Treated Patients[a]

	Unmatched		Matched	
	ALCYONE VMP (n = 354)	VISTA VMP (n = 340)	ALCYONE VMP (n = 277)	VISTA VMP (n = 276)
All-grade hematologic AEs				
Anemia	132 (37.3)	149 (43.8)	99 (35.7)	121 (43.8)
Thrombocytopenia	190 (53.7)	181 (53.2)	146 (52.7)	142 (51.4)
Neutropenia	186 (52.5)	165 (48.5)	138 (49.8)	141 (51.1)
All-grade nonhematologic AEs				
Peripheral sensory neuropathy	122 (34.5)[b]	151 (44.4)	90 (32.5)[b]	122 (44.2)
Diarrhea	87 (24.6)[b]	161 (47.4)	64 (23.1)[b]	131 (47.5)
Pyrexia	74 (20.9)[b]	101 (29.7)	50 (18.1)	76 (27.5)
Nausea	76 (21.5)[b]	165 (48.5)	52 (18.8)[b]	129 (46.7)
Infections	170 (48.0)[b]	237 (69.7)	131 (47.3)[b]	190 (68.8)
Upper respiratory tract infection	49 (13.8)	32 (9.4)	40 (14.4)	26 (9.4)
Pneumonia	17 (4.8)[b]	57 (16.8)	14 (5.1)[b]	43 (15.6)
All-grade infusion-related reactions	0[b]	4 (1.2)	0	3 (1.1)
Grade 3/4 hematologic AEs				
Anemia	70 (19.8)	63 (18.5)	53 (19.1)	52 (18.8)
Thrombocytopenia	134 (37.9)	130 (38.2)	101 (36.5)	107 (38.8)
Neutropenia	138 (39.0)	136 (40.0)	98 (35.4)	116 (42.0)
Grade 3/4 nonhematologic AEs				
Peripheral sensory neuropathy	14 (4.0)[b]	44 (12.9)	13 (4.7)[b]	33 (12.0)
Diarrhea	11 (3.1)[b]	26 (7.7)	8 (2.9)[b]	19 (6.9)
Pyrexia	2 (0.6)[b]	10 (2.9)	2 (0.7)[b]	9 (3.3)
Nausea	4 (1.1)[b]	14 (4.1)	1 (0.4)[b]	12 (4.4)
Infections	52 (14.7)	67 (19.7)	40 (14.4)	55 (19.9)
Upper respiratory tract infection	5 (1.4)	4 (1.2)	4 (1.4)	4 (1.5)
Pneumonia	14 (4.0)	28 (8.2)	11 (4.0)[b]	24 (8.7)
Grade 3/4 infusion-related reactions	0	0	0	0
Second primary cancer[c]	16 (4.5)	22 (6.5)	13 (4.7)	18 (6.5)

Values are number (%).
Abbreviation: TEAE = treatment-emergent AE.
[a]Statistical testing conducted using Cochran-Mantel-Haenszel test.
[b]$P < .05$.
[c]The assessment of secondary primary malignancies was conducted at different follow-up time points.

compared with VISTA. Additionally, matching resulted in an approximately 20% decrease in the sample size; thus, the PSM was based on a subset of the original patient cohort. Therefore, matching can only ensure 2 treatment arms are balanced with respect to measured covariates, and PSM cannot replace conducting a randomized clinical trial. Owing to minor differences in baseline characteristics between ALCYONE D-VMP and VMP, the matched VISTA VMP cohort for each comparison also differs slightly.

Conclusions

This PSM analysis demonstrates that a lower intensity VMP regimen (ie, ALYCONE VMP) has a favorable benefit/risk profile compared with the VISTA VMP schedule. Furthermore, the analysis of D-VMP and VISTA VMP shows that D-VMP significantly improves efficacy versus VISTA VMP. These findings confirm the observations of ALCYONE in which D-VMP demonstrated superiority versus VMP (PFS and ORR), using a modified bortezomib dosing schedule in both treatment arms.[18] As reflected in the HRs, the improvement in efficacy is similar to that observed in ALCYONE.[18] A recent matching adjusted indirect comparison of studies using a modified VMP versus VISTA VMP schedule demonstrated similar efficacy and a potential reduction in the rates of peripheral neuropathy,[30] supporting the use of the modified bortezomib dosing schedule for VMP. Furthermore, these findings suggest that the lower intensity VMP dosing schedule in ALCYONE did not negatively impact the efficacy of D-VMP versus

Table 6 All-Grade and Grade 3/4 TEAEs of Interest in Unmatched and Matched ALCYONE D-VMP and VISTA VMP-Treated Patients[a]

	Unmatched		Matched	
	D-VMP (n = 346)	VISTA VMP (n = 340)	D-VMP (n = 277)	VISTA VMP (n = 277)
All-grade hematologic AEs				
Anemia	104 (30.1)[b]	149 (43.8)	86 (31.1)[b]	122 (44.0)
Thrombocytopenia	171 (49.4)	181 (53.2)	139 (50.2)	145 (52.3)
Neutropenia	173 (50.0)	165 (48.5)	137 (49.5)	138 (49.8)
All-grade nonhematologic AEs				
Peripheral sensory neuropathy	98 (28.3)[b]	151 (44.4)	78 (28.2)[b]	125 (45.1)
Diarrhea	91 (26.3)[b]	161 (47.4)	78 (28.2)[b]	133 (48.0)
Pyrexia	87 (25.1)	101 (29.7)	72 (26.0)	80 (28.9)
Nausea	74 (21.4)[b]	165 (48.5)	56 (20.2)[b]	131 (47.3)
Infections	249 (72.0)	237 (69.7)	200 (72.2)	186 (67.2)
Upper respiratory tract infection	100 (28.9)[b]	32 (9.4)	86 (31.1)[b]	26 (9.4)
Pneumonia	58 (16.8)	57 (16.8)	49 (17.7)	44 (15.9)
All-grade infusion-related reactions	99 (28.6)[b]	4 (1.2)	82 (29.6)[b]	4 (1.4)
Grade 3/4 hematologic AEs				
Anemia	59 (17.1)	63 (18.5)	48 (17.3)	52 (18.8)
Thrombocytopenia	120 (34.7)	130 (38.2)	99 (35.7)	106 (38.3)
Neutropenia	138 (39.9)	136 (40.0)	108 (39.0)	112 (40.4)
Grade 3/4 nonhematologic AEs				
Peripheral sensory neuropathy	5 (1.4)[b]	44 (12.9)	3 (1.1)[b]	37 (13.4)
Diarrhea	9 (2.6)[b]	26 (7.7)	9 (3.3)	18 (6.5)
Pyrexia	2 (0.6)[b]	10 (2.9)	2 (0.7)	7 (2.5)
Nausea	3 (0.9)[b]	14 (4.1)	2 (0.7)[b]	10 (3.6)
Infections	87 (25.1)	67 (19.7)	72 (26.0)[b]	50 (18.1)
Upper respiratory tract infection	8 (2.3)	4 (1.2)	5 (1.8)	4 (1.4)
Pneumonia	43 (12.4)	28 (8.2)	35 (12.6)	22 (7.9)
Grade 3/4 infusion-related reactions	18 (5.2)[b]	0	16 (5.8)[b]	0
Second primary cancer[c]	15 (4.3)[b]	22 (6.5)	11 (4.0)	17 (6.1)

Values are number (%).
Abbreviation: TEAE = treatment-emergent AE.
[a]Statistical testing conducted using Cochran-Mantel-Haenszel test.
[b]$P < .05$.
[c]The assessment of secondary primary malignancies was conducted at different follow-up time points.

VISTA VMP,[16] while also mitigating incidence of peripheral neuropathy, an AE frequently associated with bortezomib.

Clinical Practice Points

- The phase III VISTA trial established the standard bortezomib dosing schedule for bortezomib, melphalan, and prednisone (VMP), standard of care for transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients.
- The bortezomib dosing schedule is consistent with the US prescribing information and European summary of product characteristics.
- Subsequent studies have shown that reduced intensity, subcutaneous bortezomib administration reduces bortezomib-associated toxicity without sacrificing efficacy.
- The phase III ALCYONE study of VMP ± daratumumab (D) versus VMP investigated a less intensive, modified VMP dosing schedule and subcutaneous bortezomib formulation to mitigate bortezomib-associated toxicity.
- In ALCYONE, D-VMP demonstrated improved progression-free survival (PFS) and overall response rate (ORR) versus VMP.
- Recently, D-VMP was approved by the US FDA and European Medicines Agency for transplant-ineligible NDMM patients.
- A propensity score-matched analysis, controlling for differences in baseline covariates between studies, indirectly compared VMP in ALCYONE (± D) with VMP in VISTA.
- The ALCYONE modified VMP regimen (± D) resulted in significantly lower rates of grade 3/4 peripheral sensory neuropathy versus VISTA VMP with or without matching baseline characteristics.

- After matching, the median PFS and ORR were comparable for ALCYONE VMP and VISTA VMP, and significantly improved with ALCYONE D-VMP versus VISTA VMP.
- A lower intensity VMP regimen such as in ALCYONE, with subcutaneous bortezomib administration, has a favorable benefit/risk profile compared with the VISTA standard VMP dosing schedule and intravenous bortezomib administration.
- D-VMP significantly improved efficacy versus VISTA VMP, confirming observations of ALCYONE.
- These findings support use of the modified bortezomib dosing schedule for VMP + D for transplant-ineligible NDMM patients.

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