



Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Standard of Care in Latin America for Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Propensity Score Matching Analysis

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ABSTRACT

Introduction: The phase 3 ALCYONE study demonstrated significantly longer progression-

free and overall survival (PFS/OS) and higher overall response rates (ORR) with daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) versus VMP alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). In Latin America, bortezomib- or thalidomide-based regimens remain standard of care (SoC) for this population. No head-to-head trials have compared D-VMP with SoC regimens used in Latin America.

Methods: Propensity score matching (PSM) was used to control for baseline differences between patient populations and compare outcomes for D-VMP versus SoC regimens used in Latin America. Data for the D-VMP cohort were from the D-VMP arm of the ALCYONE trial ($n = 350$). Data for the SoC cohort were from the retrospective, observational Hemato-Oncology Latin America (HOLA) study, which included patients with NDMM who did not receive a transplant ($n = 729$). Propensity scores were estimated using logistic regression. Exact, optimal, and nearest-neighbor PSM were applied to pick the best-performing method. Doubly robust estimation was the base case, since some baseline imbalances persisted.

Results: All 350 patients from the D-VMP arm of ALCYONE were included in OS/PFS analyses and 338 in ORR analysis; 478 and 324 patients, respectively, from HOLA were included in these analyses. Naïve comparison revealed important differences in baseline characteristics (age,

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chronic kidney disease, hypercalcemia, and International Staging System [ISS] stage). After nearest-neighbor matching, baseline characteristics, except ISS stage, were well balanced; comparisons favored D-VMP over SoC for OS (hazard ratio = 0.41; 95% confidence interval [CI] 0.25–0.66; $P = 0.002$) and PFS (hazard ratio = 0.48; 95% CI 0.35–0.67; $P < 0.001$). After exact matching, imbalances remained in age and ISS stage; comparisons favored D-VMP over SoC for ORR (odds ratio = 5.44; 95% CI 2.65–11.82; $P < 0.001$).

Conclusion: In transplant-ineligible patients with NDMM, D-VMP showed superior effectiveness versus bortezomib- and thalidomide-based regimens, supporting adoption of daratumumab-containing regimens in Latin America.

Keywords: ALCYONE; Daratumumab; Hemato-Oncology Latin America; Indirect treatment comparison; Latin America; Multiple myeloma; Propensity score matching

Key Summary Points

Why carry out this study?

The phase 3 ALCYONE study showed improved clinical outcomes with daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) versus VMP alone in transplant-ineligible patients with newly diagnosed multiple myeloma.

In Latin America, where uptake of novel MM treatments has been slow, standard of care treatment for this population includes bortezomib- or thalidomide-based regimens.

Since no head-to-head trials have compared D-VMP with bortezomib- or thalidomide-based regimens used in Latin America, we conducted a propensity score matching analysis to assess outcomes with D-VMP in the ALCYONE trial versus standard of care treatments in the retrospective, observational Hemato-Oncology Latin America study.

What was learned from the study?

After matching, D-VMP showed longer progression-free and overall survival and higher overall response rates versus standard of care regimens used in Latin America.

These findings support the adoption of daratumumab-containing regimens for transplant-ineligible patients with newly diagnosed multiple myeloma in this region.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13019576>.

INTRODUCTION

In many parts of the world, the treatment landscape for multiple myeloma (MM) has changed substantially following the introduction of novel agents. In patients with newly diagnosed MM (NDMM) who are not eligible for autologous stem-cell transplant (ASCT), treatment with a combination of bortezomib, melphalan, and prednisone (VMP); bortezomib, lenalidomide, and dexamethasone (VRd); or lenalidomide and dexamethasone (Rd) were historically considered standard of care (SoC) [1–3].

Adding novel targeted agents to these SoC regimens is an emerging treatment strategy supported by evidence from phase 3 clinical trials of patients with NDMM who are transplant ineligible. The addition of daratumumab, a monoclonal antibody targeting CD38, to VMP or Rd significantly improved progression-free survival (PFS) and overall response rate (ORR) in the ALCYONE [4] and MAIA [5] studies, respectively, in this patient population. In ALCYONE, overall survival (OS) was also

significantly longer with daratumumab plus VMP (D-VMP) compared with VMP alone [6].

In Latin America, the uptake of novel treatments for MM has been slow, in part due to economic constraints and the existence of separate regulatory agencies for each nation in the region [7, 8]. Although there is variability between, and sometimes within, countries, bortezomib- or thalidomide-based regimens are generally considered SoC for transplant-ineligible patients with NDMM in Latin America [9].

To date, there have been no randomized clinical trials that compared the efficacy of D-VMP with the SoC regimens used in Latin America. As a result of differences in patient characteristics between treatment populations, indirect comparisons of published aggregated clinical trial data can be subject to confounding bias, making it difficult to draw valid conclusions. Statistical methods, however, can be used to control for these baseline differences and estimate the relative treatment effect of different regimens in the absence of a head-to-head trial; when patient-level data of both comparators are available, propensity score matching (PSM) is one such method [10].

Here, we report the results of a PSM analysis comparing the effectiveness of D-VMP with that of the SoC regimens used in Latin America in transplant-ineligible patients with NDMM.

METHODS

Data Sources

Data for the D-VMP cohort were from the phase 3 ALCYONE study (ClinicalTrials.gov identifier NCT02195479), which enrolled 706 patients with NDMM who were ineligible for ASCT from 162 sites in 25 countries between February 9, 2015 and July 14, 2016 [4, 6]. Patients were randomized to receive open-label VMP alone ($n = 356$) or in combination with daratumumab (D-VMP; $n = 350$) for up to nine cycles. Dosing for all patients was as follows: subcutaneously administered bortezomib (1.3 mg/m^2 , twice weekly on weeks 1, 2, 4, and 5 of cycle 1 and once weekly on weeks 1, 2, 4, and 5 of cycles 2–9), orally administered

melphalan (9 mg/m^2 , once daily on days 1–4 of each cycle), and orally administered prednisone (60 mg/m^2 , once daily on days 1–4 of each cycle). In the D-VMP group, intravenously administered daratumumab (16 mg/kg) and orally or intravenously administered dexamethasone (20 mg) were given once weekly in cycle 1 and every 3 weeks in cycles 2–9; after cycle 9, daratumumab was administered every 4 weeks until disease progression or unacceptable toxic effects. Dexamethasone 20 mg was substituted for prednisone on day 1 of each cycle. The ALCYONE study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice guidelines, independent ethics committees or institutional review boards at each site approved the protocol, and all patients provided written informed consent. The data used for the present analysis were based on a pre-specified interim analysis for OS with a cutoff date of June 24, 2019, and a median follow-up of 40.1 months [6].

Data for the SoC cohort were from the retrospective, observational HOLA (Hemato-Oncology Latin America) study (ClinicalTrials.gov identifier NCT02559583) of patients diagnosed with selected hematologic malignancies between January 1, 2008 and December 31, 2015, and seen in 30 sites across seven countries in Latin America [9]. In the MM cohort, patients were required to be at least 18 years of age at diagnosis and have follow-up data for at least 1 year following diagnosis or until death. The present analysis included the subset of patients who did not receive ASCT ($n = 729$). The study period ended on December 31, 2016; in the overall MM population, the median length of follow-up following initiation of the first line of treatment was 26.5 months. The HOLA study was reviewed and approved by each participating hospital's independent ethics committee or institutional review board. Because the study was a retrospective chart review that presented minimal risk of harm to patients, at most sites a waiver of informed consent was granted. At sites where a waiver was not granted, the study included only patients who provided written informed consent.

Covariates

The following covariates were identified for matching and adjusting based on commonly reported variables and the opinion of clinical experts: age, sex, International Staging System (ISS) stage, chronic kidney disease (defined as a diagnosis of renal disease or serum creatinine > 2.0 mg/dL), and hypercalcemia (defined as serum calcium > 10.5 mg/dL).

Propensity Score Matching

PSM was used to correct for differences in patient baseline characteristics in the ALCYONE and HOLA studies. In line with guidance from the National Institute for Health and Care Excellence (NICE) [11], various comparative methodologies were explored (naïve comparison, multivariate-adjusted comparison, comparison of matched samples, doubly robust estimation [multivariate-adjusted comparison on matched samples], and comparison using stabilized inverse probability of treatment weighting).

Several types of PSM methods (exact, optimal, and nearest neighbor) were applied to pick the best-performing method. For each method, the distribution of propensity scores before and after matching and the postmatch balance between treatment groups (D-VMP or SoC) was assessed for the degree of overlap. To determine how adequately PSM balanced the covariates, pre- and postmatch balance between treatment groups was assessed using standardized differences for included covariates, with values greater than 0.1 suggesting potentially important imbalances [12]. Additionally, chi-square tests were performed to assess the statistical significance of differences in covariates between treatment groups before and after matching [12, 13]. This assessment determined that the best-performing PSM method for the analysis of OS and PFS was nearest-neighbor matching, whereas the best-performing method for the analysis of ORR was exact matching. Exact matching matches each case unit to all possible control units with exactly the same values for all covariates. Propensity scores were estimated

using logistic regression, and matching was performed using the MatchIt R package [14].

Propensity score distributions in matched and unmatched patients were assessed to determine whether the individuals not matched were in some specific part of the propensity score continuum. After excluding unmatched samples, outcomes observed in the matched sample were compared directly using a suitable measure of treatment effect for different endpoints (as in the naïve comparison).

Analysis Variables and Statistical Methodology

The endpoints included in the PSM analysis were OS, PFS, and ORR. There was some imbalance in baseline characteristics before matching; after matching, some imbalances persisted. For time-to-event outcomes (OS and PFS) in the matched sample, treatment effect was estimated using a Cox proportional hazards model stratified on the matched pairs and adjusted with variables with standardized mean differences greater than 0.1. Hazard ratios (HRs) for PFS and OS with two-sided 95% confidence intervals (CIs) and *P* values based on the Wald test are reported. ORR was analyzed on the basis of an odds ratio (OR) derived from a logit model. As a result of missing baseline values, the data set from each study used for the analysis of ORR was a subset of that used for OS and PFS.

RESULTS

OS and PFS Analyses

All 350 patients with transplant-ineligible NDMM who were randomized to receive D-VMP in ALCYONE were included in the analyses of OS and PFS. Of 729 patients who received SoC and had not undergone ASCT in HOLA, 478 were included; 251 patients were excluded due to missing baseline data (Fig. 1). After matching, 208 patients in each cohort were included in the OS and PFS analyses (Table 1). The most common treatment regimens in patients with NDMM in the HOLA study who did not receive

ASCT were thalidomide plus corticosteroids (32.1%) and thalidomide plus an alkylating agent (18.4%); after matching, proportions of these regimens were 23.6% and 27.9%, respectively.

Baseline characteristics for the analyses of OS and PFS before and after matching D-VMP to SoC are summarized in Table 2. Before matching for the D-VMP versus SoC comparison, there were potentially important imbalances among baseline characteristics, including age, chronic kidney disease, hypercalcemia, and ISS stage. After matching, the groups were balanced on all covariates of interest (all estimated absolute standardized differences were less than 0.1) except for ISS stage (absolute standardized difference = 0.163), which was included in the regression analysis; chi-square test results were nonsignificant ($P > 0.05$). By visual inspection, the overlap between the propensity score distribution in treatment groups improved after matching.

Figure 2 shows the Kaplan–Meier OS curves for the D-VMP versus SoC groups before and

after matching. Before matching, median OS for the D-VMP group was not reached versus 52.8 months (95% CI 46.5–76.4) for the SoC group. Naïve comparisons between groups significantly favored D-VMP over SoC for OS, with an HR of 0.51 (95% CI 0.40–0.66; $P < 0.001$). After matching, median OS for the D-VMP group was not reached versus 52.0 months (95% CI 44.3–68.6) for the SoC group, and the base case HR for OS was 0.41 (95% CI 0.25–0.66; $P = 0.002$).

Figure 3 shows the Kaplan–Meier PFS curves for the D-VMP versus SoC groups before and after matching. Before matching, median PFS for the D-VMP group was 36.4 months (95% CI 32.2–45.9) versus 15.0 months (95% CI 13.4–17.3) for the SoC group. Naïve comparisons between groups significantly favored D-VMP over SoC for PFS, with an HR of 0.45 (95% CI 0.38–0.54; $P < 0.001$). After matching, median PFS was 37.7 months (95% CI 32.0–not reached) for the D-VMP group and 18.1 months (95% CI 15.0–23.1) for the SoC group. The base

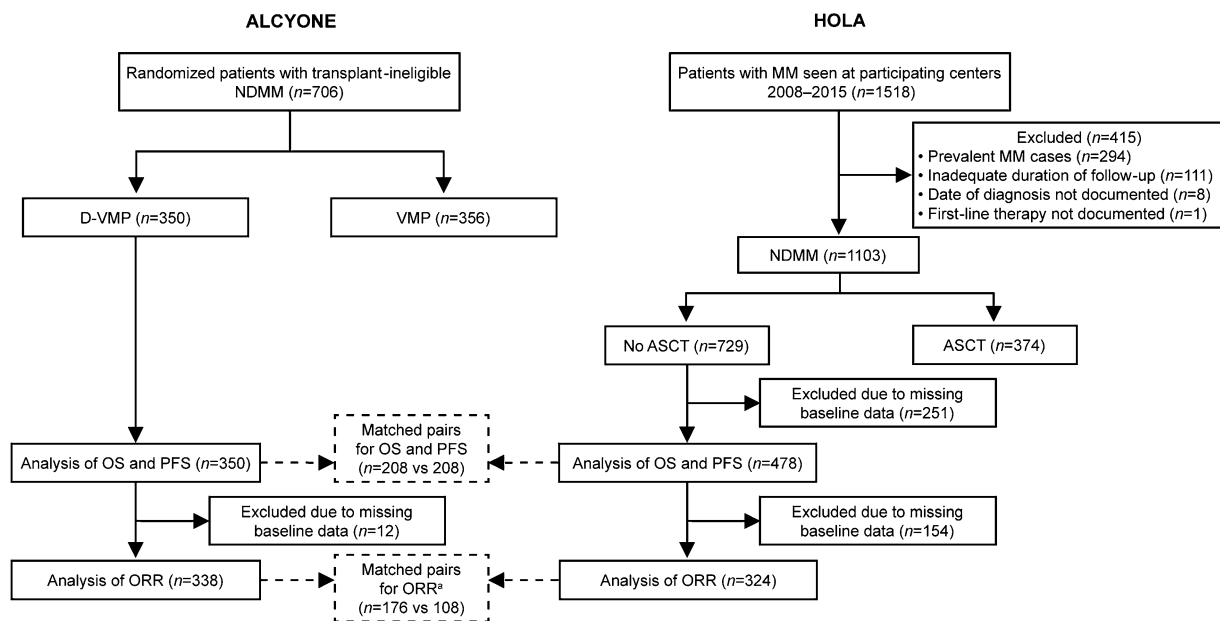


Fig. 1 Participants from ALCYONE and HOLA included in PSM analysis. ^aExact matching. ASCT autologous stem-cell transplant, D-VMP daratumumab in combination with bortezomib, melphalan, and prednisone, MM multiple myeloma, NDMM newly diagnosed

multiple myeloma, ORR overall response rate, OS overall survival, PFS progression-free survival, PSM propensity score matching, VMP bortezomib, melphalan, and prednisone

Table 1 Treatment regimens in the HOLA study before and after matching (PFS/OS analyses)

Treatment regimen, <i>n</i> (%)	Unmatched patient population (<i>n</i> = 729)	Matched patient population ^a (<i>n</i> = 208)
Thalidomide plus corticosteroids	234 (32.1)	49 (23.6)
Thalidomide plus alkylating agent	134 (18.4)	58 (27.9)
Bortezomib plus corticosteroids	103 (14.1)	24 (11.5)
CTd	74 (10.2)	23 (11.1)
Alkylating agent-based plus corticosteroids	65 (8.9)	24 (11.5)
CyBord	36 (4.9)	4 (1.9)
VAD	33 (4.5)	8 (3.8)
VMP	21 (2.9)	11 (5.3)
VTd	10 (1.4)	2 (1.0)
Other ^b	19 (2.6)	5 (2.4)

CTd cyclophosphamide, thalidomide, and dexamethasone, *CyBord* cyclophosphamide, bortezomib, and dexamethasone, *OS* overall survival, *PFS* progression-free survival, *VAD* vincristine, doxorubicin, and dexamethasone, *VMP* bortezomib, melphalan, and prednisone, *VTd* bortezomib, thalidomide, and dexamethasone

^a Nearest-neighbor matching with caliper 5%

^b Includes lenalidomide-based regimens and others

case HR for PFS was 0.48 (95% CI 0.35–0.67; *P* < 0.001).

Sensitivity analyses for OS and PFS using other comparative methodologies were also statistically significant in favor of D-VMP (Fig. 4).

ORR Analysis

After exclusion of patients with missing baseline characteristics, 338 patients in the D-VMP arm of ALCYONE and 324 who received SoC in HOLA were included in the analysis of ORR (Fig. 1). After matching, 176 patients in the

D-VMP cohort and 108 in the SoC cohort were included.

Baseline characteristics for the analysis of ORR before and after matching D-VMP to SoC are summarized in Table 3. Before matching for the D-VMP versus SoC comparison, there were potentially important imbalances in age, chronic kidney disease, hypercalcemia, and ISS stage. After matching, the groups were balanced on all covariates of interest with the exception of age (absolute standardized difference = 0.126) and ISS stage (absolute standardized difference = 0.265); however, chi-square test results for these imbalances were non-significant (*P* > 0.05). Visual inspection indicated that overlap between cohorts in the propensity score distribution improved after matching.

The unmatched ORR was 94% for D-VMP and 65% for SoC (OR = 8.61; 95% CI 5.40–14.46; *P* < 0.001). After matching, the base case OR for ORR was 5.44 (95% CI 2.65–11.82; *P* < 0.001). Sensitivity analyses using other comparative methodologies were also statistically significant in favor of D-VMP (Fig. 5).

DISCUSSION

The addition of novel agents such as daratumumab to regimens such as VMP and Rd has been shown to be effective and well tolerated in randomized clinical trials of transplant-ineligible patients with NDMM [4–6]. Accordingly, such treatment strategies are becoming more common in many countries; however, this practice has yet to be widely adopted in Latin America, where SoC regimens rely on bortezomib and thalidomide. In the absence of a head-to-head comparison of D-VMP with the SoC regimens used in Latin America, a PSM analysis was conducted to estimate the relative effectiveness of these treatments. This methodology adjusted for baseline imbalances that might affect outcomes and treatment assignments; this reduces the impact of confounding and strengthens the validity of findings [15, 16]. In this PSM analysis, D-VMP showed superior effectiveness compared with bortezomib- and thalidomide-based regimens that are commonly

Table 2 Key patient baseline characteristics for SoC and D-VMP before and after matching (PFS/OS analyses)

Variable	Unmatched patient population			Matched patient population ^a		
	SoC (<i>n</i> = 729)	D-VMP (<i>n</i> = 350)	Absolute standardized difference	SoC (<i>n</i> = 208)	D-VMP (<i>n</i> = 208)	Absolute standardized difference
Age (years), mean	63.9	71.3	0.790 ^b	70.2	70.5	0.047
Male (%)	50.6	45.7	0.098	46.6	50.0	0.067
Chronic kidney disease (%)	33.1	1.4	0.922 ^b	2.9	2.4	0.030
Hypercalcemia (%)	20.0	11.4	0.238 ^b	13.9	16.3	0.067
ISS stage ^c (%)						
I	17.2	19.7	0.269 ^b	22.1	16.3	0.163 ^b
II	29.3	39.7	NA	38.0	37.5	NA
III	53.6	40.6	NA	39.9	46.2	NA

D-VMP daratumumab in combination with bortezomib, melphalan, and prednisone, *ISS* International Staging System, *NA* not analyzed, *OS* overall survival, *PFS* progression-free survival, *SoC* standard of care

^a Nearest-neighbor matching with caliper 5%

^b Standardized differences > 0.1 suggest potentially important imbalances

^c Denominator in the SoC group based on population excluding patients with missing baseline data (*n* = 478)

used as SoC in Latin America in transplant-ineligible patients with NDMM. In a naïve comparison and propensity score matched analyses of the VMP arm of ALCYONE and the SoC group of HOLA, there were no statistically significant differences in PFS (data not shown), indicating that the improvements in effectiveness are due to the addition of daratumumab to VMP.

Several challenges have been identified for the management of patients with MM in Latin America. In an internet-based questionnaire of regional MM reference centers [7] and a subsequent survey of hematologists from 15 Latin American countries [8], variation in access to diagnostic tests and treatments in public versus private centers was reported. Similar to the findings of the HOLA study [9], bortezomib- and thalidomide-based regimens were reported as common first-line treatment options for transplant-ineligible patients with NDMM [7, 8]. As of 2018, daratumumab had been approved for MM in eight Latin American

countries (in four countries for relapsed refractory MM only); however, access is limited because of reimbursement and local policies [8, 17]. Of note, patients with MM who were treated at public centers in Mexico were more likely to be diagnosed with advanced-stage disease and have poorer outcomes than those treated at private centers [18]. Reduced disparity between public and private centers and increased access to new treatments are needed to improve patient care in this region. The results presented here support the adoption of daratumumab-containing regimens in Latin America.

There were key differences between the ALCYONE and HOLA populations that resulted in marked reductions in matched sample sizes compared with the initial cohorts. The proportion of patients who were aged 65 years or more was 90% in the D-VMP arm of ALCYONE [4] but only 51% in the cohort of patients who did not receive ASCT in HOLA [9]. Patients evaluated in the HOLA study may not have received ASCT

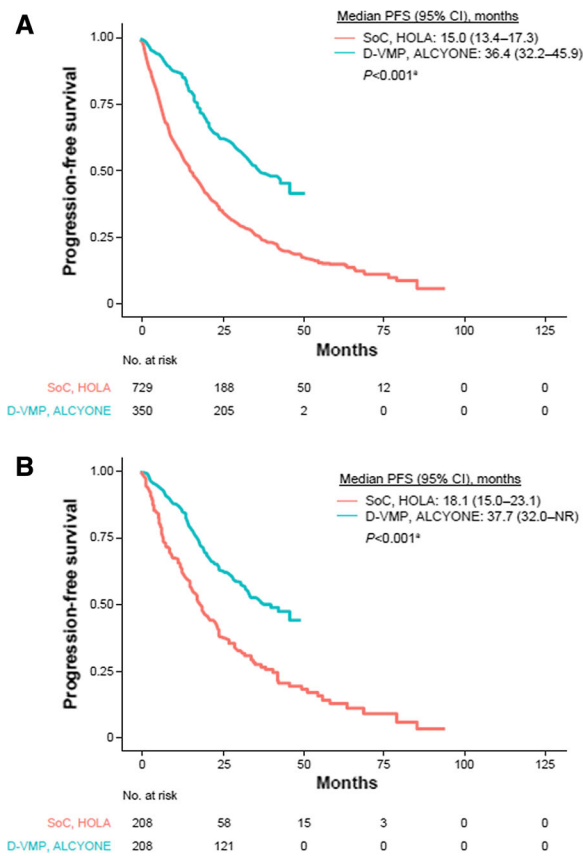
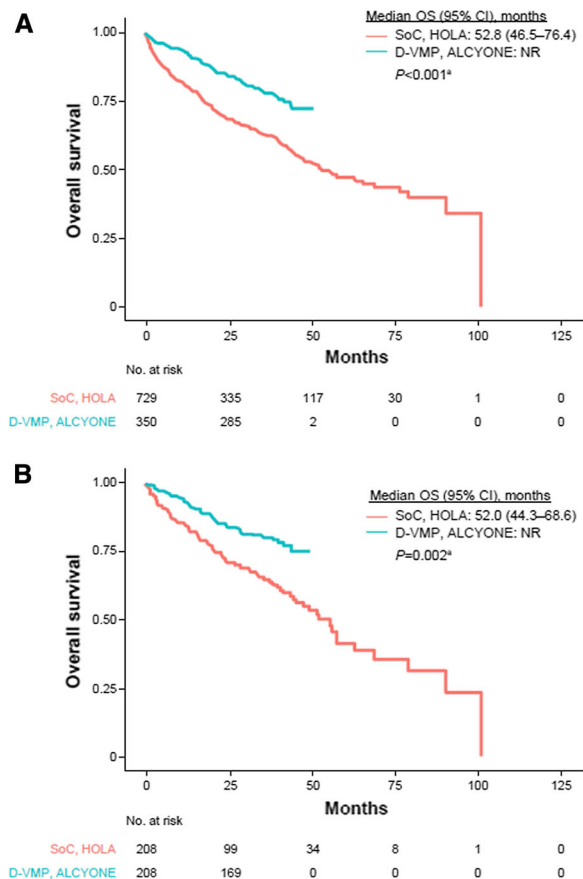


Fig. 2 Kaplan–Meier curves of (a) naïve and (b) matched sample comparisons of OS. ^aWald test. CI confidence interval, D-VMP daratumumab in combination with bortezomib, melphalan, and prednisone, NR not reached, OS overall survival, SoC standard of care

Fig. 3 Kaplan–Meier curves of (a) naïve and (b) matched sample comparisons of PFS. ^aWald test. CI confidence interval, D-VMP daratumumab in combination with bortezomib, melphalan, and prednisone, NR not reached, PFS progression-free survival, SoC standard of care

because of underlying medical issues (60% had at least one selected comorbidity documented [9]) and/or because of inconsistent access to ASCT in different Latin American countries [7, 8], rather than because of age.

Analyses based on propensity scores do have some limitations that must be considered when interpreting these findings. In this example, the performance of PSM was not optimal. Regression on matched pairs was conducted to address imbalance on the matching variables. In addition, residual confounding is possible for cross-study comparisons, especially when comparing randomized clinical trials with real-world study results. Patient management, treatment compliance, response assessment, response criteria,

and loss to follow-up may differ between these two settings. Patients in randomized clinical trials are more homogenous and receive better SoC than in the real-world setting; since real-world data for D-VMP are lacking, the performance of this regimen in the clinical trial versus real-world setting cannot be equalized. In this analysis, matching was limited by the availability and quality of the data available for patients from the HOLA study (age, sex, ISS stage, chronic kidney disease, and hypercalcemia), which may result in information bias. Other prognostic factors, including Eastern Cooperative Oncology Group performance status, myeloma type, and cytogenetic risk could not be adjusted for, as these were not consistently available in the HOLA registry.

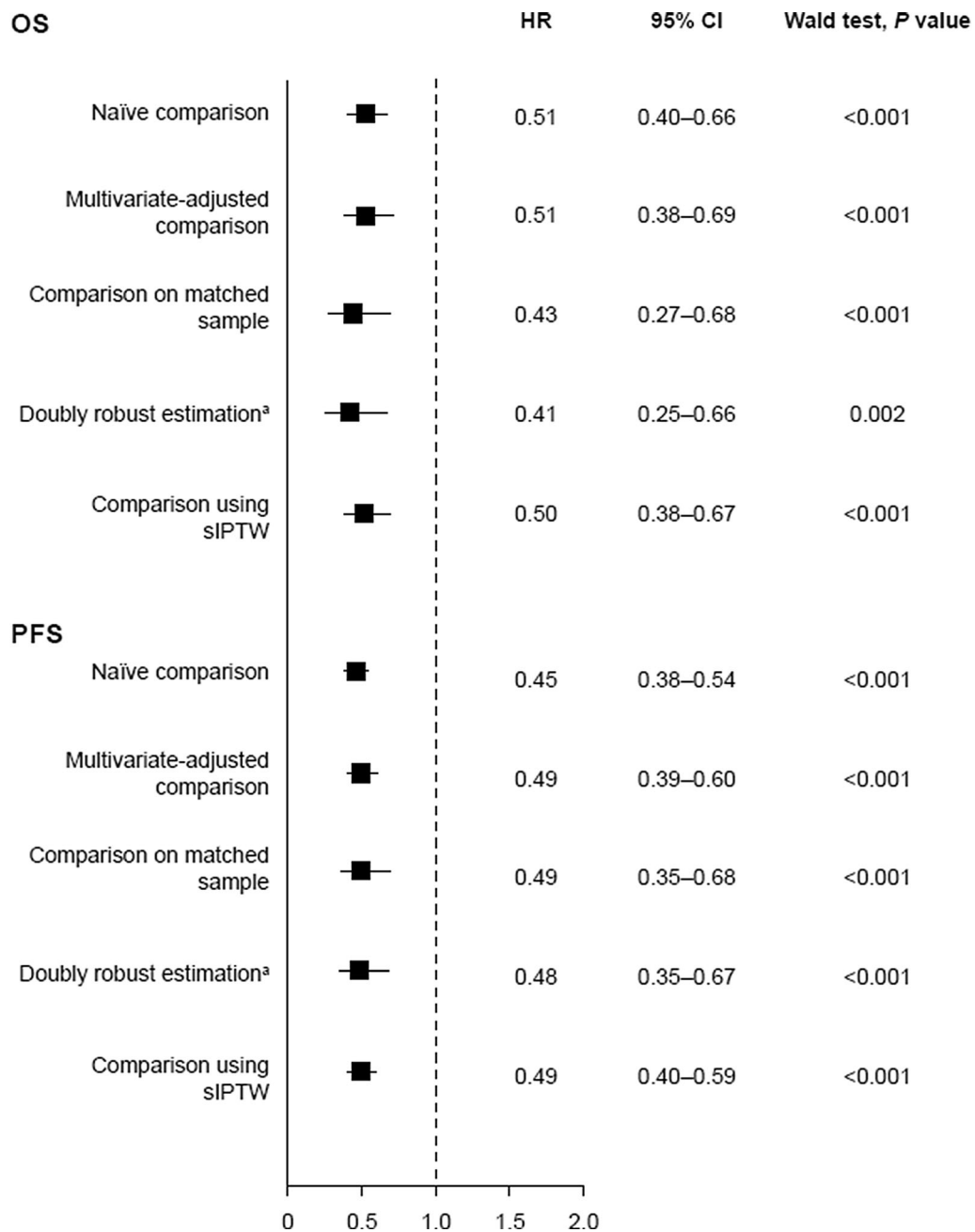


Fig. 4 HRs for OS and PFS before and after matching. HRs < 1 favor D-VMP; HRs > 1 favor SoC. ^aBase case. CI confidence interval, D-VMP daratumumab in combination with bortezomib, melphalan, and prednisone, HR

hazard ratio, OS overall survival, PFS progression-free survival, sIPTW stabilized inverse probability treatment weighting, SoC standard of care

Additionally, there is the potential for selection bias, as patients from the HOLA study represented a sample specifically selected for Latin America and less than 2% of the patients in the

ALCYONE study were from Latin America. Finally, some imbalances in baseline characteristics persisted after matching. Although these imbalances were not significant, it is possible

Table 3 Key patient baseline characteristics for SoC and D-VMP before and after matching (ORR analysis)

Variable	Unmatched patient population		Matched patient population (nearest with caliper 5%)		Matched patient population (exact matching)	
	SoC (n = 324)	D-VMP (n = 338)	SoC (n = 148)	D-VMP (n = 148)	SoC (n = 108)	D-VMP (n = 176)
Age (years), mean	64.4	71.3	69.8	69.8	69.1	69.8
Male (%)	50.3	45.9	45.9	35.8	46.3	43.8
Chronic kidney disease (%)	34.0	1.2	3.4	2.7	1.9	1.1
Hypercalcemia (%)	24.4	11.8	15.5	8.1	6.5	4.5
ISS stage (%)						
I	18.5	20.1	24.3	36.5	18.5	22.2
II	30.6	40.2	35.1	18.9	33.3	42.6
III	50.9	39.6	40.5	44.6	48.1	35.2
Absolute standardized difference						
		0.747 ^a				
				0.002		
						0.126 ^a
		0.089		0.207 ^a		0.051
		0.954 ^a		0.039		0.059
		0.330 ^a		0.232 ^a		0.085
		0.238 ^a		0.395 ^a		0.265 ^a
		NA		NA		NA
		NA		NA		NA

*D-I/M*P daratumumab in combination with bortezomib, melphalan, and prednisone, *ISS* International Staging System, *NA* not analyzed, *ORR* overall response rate, *SoC* standard of care

^a Standardized differences > 0.1 suggest potentially important imbalances

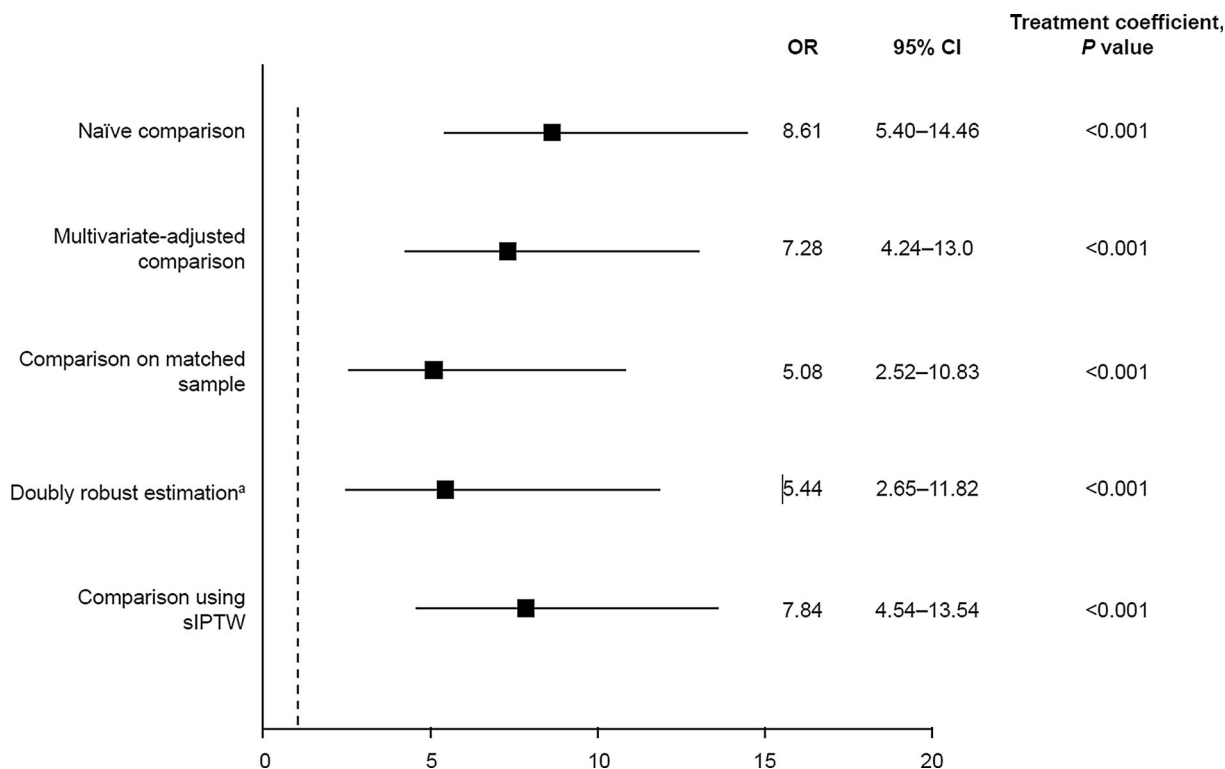


Fig. 5 ORs for ORR before and after matching. ORs < 1 favor SoC; ORs > 1 favor D-VMP. ^aBase case. CI confidence interval, D-VMP daratumumab in combination with bortezomib, melphalan, and prednisone, OR

odds ratio, ORR overall response rate, sIPTW stabilized inverse probability treatment weighting, SoC standard of care

that they introduced bias in the indirect comparison.

In addition to limitations related to the PSM methodology, it should be noted that the HOLA study, which evaluated patients diagnosed with MM between 2008 and 2015, may not be fully representative of current treatment patterns in Latin America, although it is the most recent data set available for this population. Nevertheless, the HOLA study was considered a valid source for this analysis given the large sample size and the acquisition of data for patient characteristics, treatments, and effectiveness outcomes.

CONCLUSIONS

This PSM analysis demonstrated significant OS, PFS, and ORR benefits with D-VMP over SoC in Latin America, which primarily includes

bortezomib- and thalidomide-based regimens, in patients with NDMM who are transplant ineligible. These findings may aid physicians in improving treatment strategies for this patient population in Latin America, as approval and access to newer targeted drugs increases in this region.

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Authorship Contributions. Vania Hungria and Deborah M. Martínez-Baños enrolled patients, acquired data, and interpreted data for the HOLA study. María-Victoria Mateos and Meletios A. Dimopoulos participated in trial design, enrolled patients, acquired data, and interpreted data for the ALCYONE study. Michele Cavo enrolled patients and acquired data for the ALCYONE study. Bart Heeg and Andrea Garcia performed the PSM analyses and data interpretation. Annette Lam, Gerardo Machnicki, Jianming He, and Mariana Fernandez designed the PSM analysis and interpreted the data. Gerardo Machnicki interpreted data for the HOLA study. All authors contributed to drafting of the manuscript and provided final approval for submission.

Disclosures. Vania Hungria served as an advisory board participant or member of Board of Directors (AbbVie, Amgen, Celgene, Janssen, and Takeda), received consulting fees (AbbVie, Amgen, BMS, Celgene, Janssen, and Takeda), and received honoraria and/or served on a speakers bureau (Amgen, BMS, Celgene, Janssen, and Takeda). Deborah M. Martínez-Baños served as an advisory board participant (Amgen and Celgene). María-Victoria Mateos served as an advisory board participant or member of Board of Directors (AbbVie, Amgen,

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Compliance with Ethics Guidelines. The ALCYONE study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice guidelines, independent ethics committees or institutional review boards at each site approved the protocol, and all patients provided written informed consent. The HOLA study was reviewed and approved by each participating hospital's independent ethics committee or institutional review board. Because the study was a retrospective chart review that presented minimal risk of harm to patients, at most sites a waiver of informed consent was granted. At sites where a waiver was not granted, the study included only patients who provided written informed consent.

Data Availability. 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 Yale Open Data Access (YODA) Project site.

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