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Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Frailty Subgroup Analysis of ALCYONE

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Abstract

In the global phase 3 ALCYONE study, daratumumab plus bortezomib/melphalan/prednisone (D-VMP) significantly improved outcomes versus VMP in transplant-ineligible patients with newly diagnosed multiple myeloma. In this subgroup analysis of ALCYONE, frailty was assessed retrospectively among all randomized patients (D-VMP, *n* = 350; VMP, *n* = 356). Improved efficacy with D-VMP versus VMP was observed across frailty subgroups, with no new safety concerns.

Background: In the phase 3 ALCYONE study, daratumumab plus bortezomib/melphalan/prednisone (D-VMP) versus bortezomib/melphalan/prednisone (VMP) significantly improved progression-free survival (PFS) and overall survival (OS) in transplant-ineligible, newly diagnosed multiple myeloma (NDMM) patients. We present a subgroup analysis of ALCYONE by patient frailty status. **Patients and Methods:** Frailty assessment was performed retrospectively

Abbreviations: ADL, Activities of Daily Living; ASCT, autologous stem cell transplantation; CCI, Charlson comorbidity index; CI, confidence interval; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IADL, Instrumental Activities of Daily Living; IMWG, International Myeloma Working Group; ISS, International Staging System; NDMM, newly diagnosed multiple myeloma; NR, not reached; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event; VMP, bortezomib/melphalan/prednisone.

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using age, Charlson comorbidity index, and baseline Eastern Cooperative Oncology Group performance status score. Patients were classified as fit (0), intermediate (1), or frail (≥2); a nonfrail category combined fit and intermediate patients. **Results:** Among randomized patients (D-VMP, $n = 350$; VMP, $n = 356$), 391 (55.4%) were nonfrail (D-VMP, 187 [53.4%]; VMP, 204 [57.3%]) and 315 (44.6%) were frail (163 [46.6%]; 152 [42.7%]). After 40.1-months median follow-up, nonfrail patients had longer PFS and OS than frail patients, but benefits of D-VMP versus VMP were maintained across subgroups: PFS nonfrail (median, 45.7 vs. 19.1 months; hazard ratio [HR], 0.36; $P < .0001$), frail (32.9 vs. 19.5 months; HR, 0.51; $P < .0001$); OS nonfrail (36-month rate, 83.6% vs. 74.5%), frail (71.4% vs. 59.0%). Improved greater than or equal to complete response and minimal residual disease (10^{-5})-negativity rates were observed for D-VMP versus VMP across subgroups. The 2 most common grade 3/4 treatment-emergent adverse events were neutropenia (nonfrail: 39.2% [D-VMP] and 42.4% [VMP]; frail: 41.3% and 34.4%) and thrombocytopenia (nonfrail: 32.8% and 36.9%; frail: 36.9% and 39.1%). **Conclusion:** Our findings support the clinical benefit of D-VMP in transplant-ineligible NDMM patients enrolled in ALCYONE, regardless of frailty status.

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Introduction

Daratumumab is a human IgGκ monoclonal antibody that targets CD38 with a direct on-tumor[1-4] and immunomodulatory[5-7] mechanism of action that is approved in many countries as monotherapy and in combination with standard-of-care regimens for multiple myeloma patients.[8-17] In the primary analysis of the phase 3 ALCYONE study (median follow-up, 16.5 months), adding daratumumab to bortezomib/melphalan/prednisone (D-VMP) significantly prolonged progression-free survival (PFS) over bortezomib/melphalan/prednisone (VMP) and induced deep responses in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients.[10] After a median follow-up of 40.1 months, D-VMP continued to show significant PFS benefit and significantly prolonged overall survival (OS), even in patients aged ≥75 years.[18] However, older patients vary in fitness levels.[19,20] Frail patients will expectedly often have reduced tolerance to cancer treatment regimens and increased symptom burden.[20,21] Thus, a subgroup analysis based on frailty status instead of age alone is likely to be more informative.

In 2015, a frailty scoring system was developed by the International Myeloma Working Group (IMWG) that classifies patients into 3 frailty subgroups—fit, intermediate, and frail—based on age, comorbidities (Charlson comorbidity index [CCI]), and patient-evaluated self-care (Katz Activities of Daily Living [ADL] scale) and household management (Lawton Instrumental Activities of Daily Living [IADL] scale) assessments.[20] However, not all clinical trials assess patients using the ADL and IADL scales, including ALCYONE. Subsequently, in a retrospective subgroup analysis of the FIRST trial, a frailty scale based on age, CCI, and the physician-evaluated Eastern Cooperative Oncology Group performance status (ECOG PS) score was developed that also allows classification of patients into fit, intermediate, and frail subgroups.[19] Although the ECOG PS score is more subjective, with its susceptibility to intra-/interobserver bias, compared with the ADL and IADL scales used in the IMWG scoring system,[22] ECOG PS score is commonly assessed in clinical trials, and a frailty scale using the ECOG PS instead of the ADL and IADL scales would be more practical for clinical use. Assessments based on the CCI and ECOG PS–containing frailty scale were further simplified to classify patients into 2 subgroups—frail and nonfrail (a combination of the fit and intermediate subgroups).[19] Both 3-subgroup and 2-subgroup frailty classifications were demonstrated to be predictive measures of clinical outcomes among transplant-ineligible NDMM patients.[19,20,23]

We present a subgroup analysis of patients in ALCYONE comparing D-VMP versus VMP by frailty status.

Patients and Methods

Study Design and Patients

ALCYONE (ClinicalTrials.gov Identifier: NCT02195479) is a multicenter, randomized, open-label, active-controlled, phase 3 trial. The complete methodology of ALCYONE has been published previously.[10] The study was approved by independent ethics committees or institutional review boards at each site and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

Briefly, eligible patients had documented NDMM ineligible for high-dose chemotherapy with autologous stem cell transplantation because of their age (≥65 years) or comorbidities, an ECOG PS score of 0 to 2, and creatinine clearance ≥40 mL/min.

Treatment

Patients were randomized 1:1 to D-VMP or VMP. The randomization was stratified by International Staging System (ISS) disease stage (I vs. II vs. III), geographic region (Europe vs. other), and age (<75 vs. ≥75 years). All patients received up to nine 42-day cycles of bortezomib 1.3 mg/m^2 of body surface area subcutaneously 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 to 9; melphalan 9 mg/m^2 orally once daily on Days 1 to 4 of each cycle; and prednisone 60 mg/m^2 orally once daily on Days 1 to 4 of each cycle. Additionally, patients

in the D-VMP cohort received daratumumab 16 mg/kg intravenous (IV) once weekly during Cycle 1, every 3 weeks during Cycles 2 to 9, and then every 4 weeks thereafter until disease progression or unacceptable toxicity with oral or IV dexamethasone 20 mg to manage infusion-related reactions. Dexamethasone was substituted for prednisone on Day 1 of each cycle.

Frailty Evaluation

Frailty scores were calculated retrospectively for all patients using age, CCI (based on a retrospective review of each patient's medical history), and baseline ECOG PS score (Supplementary Table 1).[19] The sum of scores was used to classify patients as fit (0), intermediate (1), or frail (≥2). Those with a frailty status of fit (0) or intermediate (1) were also collectively classified as nonfrail. For OS and PFS evaluation, patients within the nonfrail and frail subgroups were further divided by ISS stage (I/II vs. III). Patients with missing data were excluded from frailty evaluation.

Assessments and Statistical Analyses

The primary endpoint was PFS; post hoc analyses were performed by patient frailty status. Efficacy endpoints were assessed in the intent-to-treat population. Safety was assessed based on the safety population (patients who received ≥1 dose of study treatment).

A log-rank test compared PFS between treatment cohorts. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with treatment as the sole explanatory variable for the frailty subgroups. The Kaplan–Meier method was used to evaluate time-to-event variables. A Cochran–Mantel–Haenszel χ^2 test was used to measure differences in overall response rate (ORR), very good partial response or better (≥VGPR) rate, complete response or better (≥CR) rate, and stringent complete response rate. A Fisher exact test was used to test treatment differences in minimal residual disease (MRD)-negativity rate.

Results

Patient Disposition and Treatment

Frailty scores were calculated retrospectively for each randomized patient (D-VMP, $n = 350$; VMP, $n = 356$); 17.3% of patients were classified as fit (D-VMP, 13.7%; VMP, 20.8%), 38.1% were intermediate (39.7%; 36.5%), and 44.6% were frail (46.6%; 42.7%). The total-nonfrail subgroup included 55.4% of patients (D-VMP, 53.4%; VMP, 57.3%). All fit patients received treatment. In the intermediate subgroup, 1 patient in each of the D-VMP and VMP cohorts did not receive treatment, and in the frail subgroup, 3 patients in the D-VMP cohort and 1 patient in the VMP cohort did not receive treatment. Demographics and baseline characteristics were generally balanced between the treatment cohorts within each frailty subgroup (Table 1). A higher proportion of patients in the frail subgroup was categorized as ISS stage III versus other frailty subgroups.

Patient disposition during Cycles 1 to 9 by frailty status is summarized in Table 2. During Cycles 1 to 9, a lower proportion of D-VMP–treated patients discontinued treatment versus VMP-treated patients in all frailty subgroups (fit, 4.2% vs. 24.3%; intermediate, 14.5% vs. 28.7%; total-nonfrail, 11.8% vs. 27.1%; frail, 28.8% vs. 41.7%). The 2 most common reasons for treatment discontinuation in all frailty subgroups were progressive disease and adverse events. Patients in the VMP cohort were limited to 9 cycles of treatment. During Cycles 10+, a lower proportion of patients who entered Cycle 10 discontinued treatment in the total-nonfrail subgroup versus in the frail subgroup (Supplementary Table 2). In the D-VMP cohorts, 27 (56.3%), 65 (47.1%), 92 (49.5%), and 54 (33.8%) patients in the fit, intermediate, total-nonfrail, and frail subgroups, respectively, continued to receive daratumumab monotherapy.

As expected due to study design, median (range) duration of treatment was longer with D-VMP versus VMP in all frailty subgroups (fit, 37.2 [11.2-48.3] vs. 12.0 [0.4-14.3] months, respectively; intermediate, 36.3 [0.1-50.6] vs. 12.0 [0.1-15.7] months; total-nonfrail, 36.4 [0.1-50.6] vs. 12.0 [0.1-15.7] months; frail, 24.7 [0.03-49.7] vs. 11.9 [0.2-14.2] months). The median relative dose intensity of daratumumab was similar across frailty subgroups (fit, 99.4%; intermediate, 99.3%; total-nonfrail, 99.3%; frail, 98.5%; Supplementary Table 3). The median relative dose intensities of bortezomib and melphalan were similar across frailty subgroups and between D-VMP versus VMP in all frailty subgroups (bortezomib: fit, 96.8% vs. 95.6%, respectively; intermediate, 95.6% vs. 95.0%; total-nonfrail, 95.7% vs. 95.1%; frail, 95.3% vs. 92.7%; melphalan: fit, 94.8% vs. 96.8%; intermediate, 97.7% vs. 97.2%; total-nonfrail, 97.4% vs. 97.1%; frail, 95.9% vs. 95.4%). The prednisone-equivalent median relative dose intensity was also similar across frailty subgroups and between D-VMP versus VMP in all frailty subgroups (fit, 99.2% vs. 99.0%, respectively; intermediate, 99.0% vs. 98.8%; total-nonfrail, 99.1% vs. 98.8%; frail, 99.0% vs. 98.9%).

Bortezomib dose reductions occurred in 20.8% (D-VMP) and 33.8% (VMP) of fit patients, 32.6% and 32.6% of intermediate patients, 29.6% and 33.0% of total-nonfrail patients, and 32.5% and 37.7% of frail patients. Melphalan dose reductions occurred in 20.8% (D-VMP) and 24.3% (VMP) of fit patients, 15.2% and 19.4% of intermediate patients, 16.7% and 21.2% of total-nonfrail patients, and 24.4% and 23.8% of frail patients. Prednisone-equivalent dose reductions occurred in 4.2% (D-VMP) and 6.8% (VMP) of fit patients, 5.1% and 5.4% of intermediate patients, 4.8% and 5.9% of total-nonfrail patients, and 9.4% and 6.0% of frail patients.

Efficacy

After a median follow-up of 40.1 months, the PFS benefit of D-VMP versus VMP was maintained in all frailty subgroups: fit (median, not reached [NR] vs. 22.2 months; HR, 0.34; 95% CI, 0.20-0.57), intermediate (40.1 vs. 18.3 months; HR, 0.37; 95% CI, 0.27-0.50), total-nonfrail (45.7 vs. 19.1 months; HR, 0.36; 95% CI, 0.28-0.47), and frail (32.9 vs. 19.5 months; HR, 0.51; 95% CI, 0.39-0.68); all $P < .0001$ (Figure 1A-B). PFS with D-VMP was prolonged in total-nonfrail versus frail patients, whereas PFS with VMP was similar between total-nonfrail and frail patients. The 36-month PFS rate was highest among fit patients in the D-VMP cohort and decreased with increasing frailty: fit, 59.7% (D-VMP) and 18.2% (VMP); intermediate, 54.3% and 18.5%; total-nonfrail, 55.7% and 18.5%; and frail, 44.5% and 18.6%.

Table 1 Demographics and Baseline Characteristics[a]

	Nonfrail[b]						Frail	
	Fit (17.3%[c]; *n* = 122/706)		Intermediate (38.1%[c]; *n* = 269/706)		Total-Nonfrail[b] (55.4%[c]; *n* = 391/706)		Frail (44.6%[c]; *n* = 315/706)	
	D-VMP (13.7%[d]; *n* = 48/350)	VMP (20.8%[e]; *n* = 74/356)	D-VMP (39.7%[d]; *n* = 139/350)	VMP (36.5%[e]; *n* = 130/356)	D-VMP (53.4%[d]; *n* = 187/350)	VMP (57.3%[e]; *n* = 204/356)	D-VMP (46.6%[d]; *n* = 163/350)	VMP (42.7%[e]; *n* = 152/356)
Age, years, *n* (%)								
Median (range)	70.0 (65-75)	71.0 (56-75)	71.0 (52-80)	70.0 (52-80)	70.0 (52-80)	70.0 (52-80)	74.0 (40-93)	74.0 (50-91)
<65	0	3 (4.1)	13 (9.4)	10 (7.7)	13 (7.0)	13 (6.4)	23 (14.1)	11 (7.2)
65-<75	45 (93.8)	60 (81.1)	105 (75.5)	98 (75.4)	150 (80.2)	158 (77.5)	60 (36.8)	67 (44.1)
≥75	3 (6.3)	11 (14.9)	21 (15.1)	22 (16.9)	24 (12.8)	33 (16.2)	80 (49.1)	74 (48.7)
≥80	0	0	1 (0.7)	3 (2.3)	1 (0.5)	3 (1.5)	32 (19.6)	29 (19.1)
Female, *n* (%)	25 (52.1)	34 (45.9)	77 (55.4)	74 (56.9)	102 (54.5)	108 (52.9)	88 (54.0)	81 (53.3)
ECOG PS score, *n* (%)								
0	48 (100.0)	74 (100.0)	18 (12.9)	17 (13.1)	66 (35.3)	91 (44.6)	12 (7.4)	8 (5.3)
1	0	0	121 (87.1)	113 (86.9)	121 (64.7)	113 (55.4)	61 (37.4)	60 (39.5)
2	0	0	0	0	0	0	90 (55.2)	84 (55.3)
ISS stage, *n* (%)[f]								
I	11 (22.9)	20 (27.0)	39 (28.1)	24 (18.5)	50 (26.7)	44 (21.6)	19 (11.7)	23 (15.1)
II	22 (45.8)	39 (52.7)	57 (41.0)	55 (42.3)	79 (42.2)	94 (46.1)	60 (36.8)	66 (43.4)
III	15 (31.3)	15 (20.3)	43 (30.9)	51 (39.2)	58 (31.0)	66 (32.4)	84 (51.5)	63 (41.4)
Type of measurable disease, *n* (%)[g]								
IgG	24 (50.0)	28 (37.8)	56 (40.3)	59 (45.4)	80 (42.8)	87 (42.6)	63 (38.7)	53 (34.9)
IgA	5 (10.4)	13 (17.6)	14 (10.1)	14 (10.8)	19 (10.2)	27 (13.2)	30 (18.4)	26 (17.1)
Other[h]	0	1 (1.4)	3 (2.2)	1 (0.8)	3 (1.6)	2 (1.0)	3 (1.8)	1 (0.7)
Serum and urine	11 (22.9)	23 (31.1)	40 (28.8)	35 (26.9)	51 (27.3)	58 (28.4)	40 (24.5)	47 (30.9)

(*continued on next page*)

Table 1 (*continued*)

	Nonfrail[b]						Frail	
	Fit (17.3%[c]; *n* = 122/706)		Intermediate (38.1%[c]; *n* = 269/706)		Total-Nonfrail[b] (55.4%[c]; *n* = 391/706)		Frail (44.6%[c]; *n* = 315/706)	
	D-VMP (13.7%[d]; *n* = 48/350)	VMP (20.8%[e]; *n* = 74/356)	D-VMP (39.7%[d]; *n* = 139/350)	VMP (36.5%[e]; *n* = 130/356)	D-VMP (53.4%[d]; *n* = 187/350)	VMP (57.3%[e]; *n* = 204/356)	D-VMP (46.6%[d]; *n* = 163/350)	VMP (42.7%[e]; *n* = 152/356)
Detected in urine only	7 (14.6)	6 (8.1)	16 (11.5)	13 (10.0)	23 (12.3)	19 (9.3)	20 (12.3)	18 (11.8)
Detected as serum free light-chain only	1 (2.1)	3 (4.1)	10 (7.2)	8 (6.2)	11 (5.9)	11 (5.4)	7 (4.3)	7 (4.6)
Creatinine clearance, *n* (%)								
≥90	7 (14.6)	21 (28.4)	28 (20.1)	20 (15.4)	35 (18.7)	41 (20.1)	25 (15.3)	20 (13.2)
60-<90	26 (54.2)	40 (54.1)	60 (43.2)	59 (45.4)	86 (46.0)	99 (48.5)	54 (33.1)	51 (33.6)
30-<60	15 (31.3)	13 (17.6)	50 (36.0)	49 (37.7)	65 (34.8)	62 (30.4)	82 (50.3)	75 (49.3)
<30	0	0	1 (0.7)	2 (1.5)	1 (0.5)	2 (1.0)	2 (1.2)	6 (3.9)
Cytogenetic profile[i]								
N	45	63	125	108	170	171	144	131
Standard risk, *n* (%)	38 (84.4)	54 (85.7)	112 (89.6)	90 (83.3)	150 (88.2)	144 (84.2)	111 (77.1)	113 (86.3)
High risk, *n* (%)[j]	7 (15.6)	9 (14.3)	13 (10.4)	18 (16.7)	20 (11.8)	27 (15.8)	33 (22.9)	18 (13.7)
del17p	1 (2.2)	4 (6.3)	7 (5.6)	11 (10.2)	8 (4.7)	15 (8.8)	21 (14.6)	12 (9.2)
t(4;14)	2 (4.4)	5 (7.9)	7 (5.6)	6 (5.6)	9 (5.3)	11 (6.4)	16 (11.1)	6 (4.6)
t(14;16)	4 (8.9)	3 (4.8)	0	2 (1.9)	4 (2.4)	5 (2.9)	2 (1.4)	1 (0.8)
Median time since initial diagnosis of MM (range), months	0.66 (0.3-3.2)	0.76 (0.1-7.6)	0.72 (0.1-6.4)	0.87 (0.2-5.0)	0.72 (0.1-6.4)	0.85 (0.1-7.6)	0.82 (0.2-11.4)	0.76 (0.2-24.8)

Abbreviations: D-VMP = daratumumab plus bortezomib/melphalan/prednisone; ECOG PS = Eastern Cooperative Oncology Group performance status; ISS = International Staging System; ITT = intent-to-treat; MM = multiple myeloma; VMP = bortezomib/melphalan/prednisone.

[a] Percentages in the table were calculated using the number of patients in each treatment cohort per frailty subgroup of the ITT population (fit: D-VMP, *n* = 48; VMP, *n* = 74; intermediate: D-VMP, *n* = 139; VMP, *n* = 130; total-nonfrail: D-VMP, *n* = 187; VMP, *n* = 204; frail: D-VMP; *n* = 163; VMP, *n* = 152) as the denominator, unless otherwise indicated.

[b] Nonfrail subgroup consists of fit and intermediate patients.

[c] Percentage was calculated using the number of patients in the ITT population as the denominator.

[d] Percentage was calculated using the number of patients in the D-VMP cohort of the ITT population as the denominator.

[e] Percentage was calculated using the number of patients in the VMP cohort of the ITT population as the denominator.

[f] Based on the combination of serum β2-microglobulin and albumin.

[g] Includes patients without measurable disease in serum and urine.

[h] Includes IgD, IgM, IgE, and biclonal.

[i] Cytogenetic risk was based on fluorescence in situ hybridization or karyotype analysis. Percentages were calculated using the number of patients in each treatment cohort per frailty subgroup with available baseline cytogenetic data as the denominator.

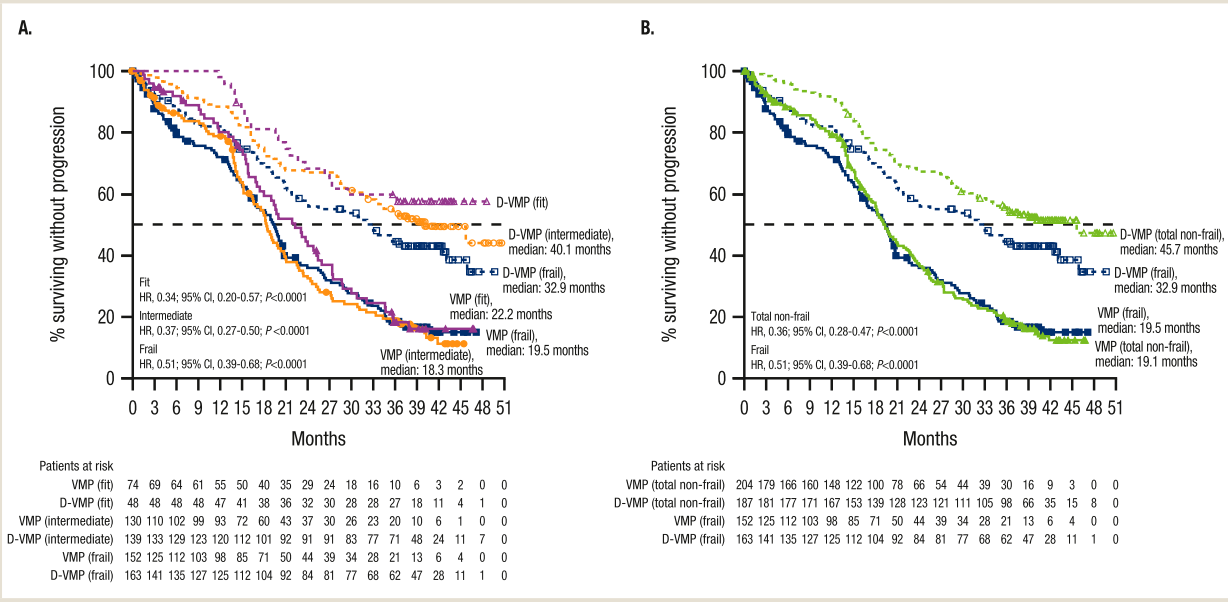
[j] Patients with high-risk cytogenetics had a del17p, t(4;14), or t(14;16) abnormality.

Table 2 Patient Disposition for Cycles 1 Through 9 (Safety Population)[a]

	Nonfrail[b]						Frail	
	Fit (17.4%[c]; *n* = 122/700)		Intermediate (38.1%[c]; *n* = 267/700)		Total-Nonfrail[b] (55.6%[c]; *n* = 389/700)		Frail (44.4%[c]; *n* = 311/700)	
	D-VMP (13.9%;[d] *n* = 48/346)	VMP (20.9%;[e] *n* = 74/354)	D-VMP (39.9%;[d] *n* = 138/346)	VMP (36.4%;[e] *n* = 129/354)	D-VMP (53.8%;[d] *n* = 186/346)	VMP (57.3%;[e] *n* = 203/354)	D-VMP (46.2%;[d] *n* = 160/346)	VMP (42.7%;[e] *n* = 151/354)
Patients who discontinued treatment, *n* (%)	2 (4.2)	18 (24.3)	20 (14.5)	37 (28.7)	22 (11.8)	55 (27.1)	46 (28.8)	63 (41.7)
Reason for discontinuation, *n* (%)								
Progressive disease	1 (2.1)	7 (9.5)	8 (5.8)	18 (14.0)	9 (4.8)	25 (12.3)	14 (8.8)	22 (14.6)
Adverse event	1 (2.1)	6 (8.1)	6 (4.3)	8 (6.2)	7 (3.8)	14 (6.9)	11 (6.9)	20 (13.2)
Noncompliance with study drug[f]	0	1 (1.4)	1 (0.7)	2 (1.6)	1 (0.5)	3 (1.5)	9 (5.6)	12 (7.9)
Death	0	0	2 (1.4)	4 (3.1)	2 (1.1)	4 (2.0)	9 (5.6)	4 (2.6)
Physician decision	0	3 (4.1)	0	1 (0.8)	0	4 (2.0)	0	3 (2.0)
Patient withdrawal	0	1 (1.4)	2 (1.4)	4 (3.1)	2 (1.1)	5 (2.5)	0	1 (0.7)
Other	0	0	1 (0.7)	0	1 (0.5)	0	3 (1.9)	1 (0.7)

Abbreviations: D-VMP = daratumumab plus bortezomib/melphalan/prednisone; VMP = bortezomib/melphalan/prednisone.
[a] Percentages in the table were calculated using the number of patients in each treatment cohort per frailty subgroup of the safety population (fit: D-VMP, *n* = 48; VMP, *n* = 74; intermediate: D-VMP, *n* = 138; VMP, *n* = 129; total-nonfrail: D-VMP, *n* = 186; VMP, *n* = 203; frail: D-VMP, *n* = 160; VMP, *n* = 151) as the denominator, unless otherwise indicated.
[b] Nonfrail subgroup consists of fit and intermediate patients.
[c] Percentage was calculated using the number of patients in the safety population as the denominator.
[d] Percentage was calculated using the number of patients in the D-VMP cohort of the safety population as the denominator.
[e] Percentage was calculated using the number of patients in the VMP cohort of the safety population as the denominator.
[f] Based on the reason "Patient refused further study treatment."

Figure 1 PFS in the (A) fit, intermediate, and frail subgroups and (B) total-nonfrail and frail subgroups. CI = confidence interval; D-VMP = daratumumab plus bortezomib/melphalan/prednisone; HR = hazard ratio; PFS = progression-free survival; VMP = bortezomib/melphalan/prednisone.



The OS benefit of D-VMP versus VMP was also maintained in all frailty subgroups: fit (median, NR vs. 46.2 months; HR, 0.18; 95% CI, 0.05-0.62; $P = .0021$), intermediate (NR in both cohorts; HR, 0.62; 95% CI, 0.39-0.98; $P = .0407$), total-nonfrail (NR in both cohorts; HR, 0.52; 95% CI, 0.34-0.79; $P = .0017$), and frail (NR in both cohorts; HR, 0.66; 95% CI, 0.46-0.96; $P = .0292$; Figure 2A-B). The 36-month OS rate was higher with D-VMP versus VMP in all frailty subgroups, with decreasing rates from fit to frail (fit, 93.8% vs. 77.4%, respectively; intermediate, 80.0% vs. 72.7%; total-nonfrail, 83.6% vs. 74.5%; frail, 71.4% vs. 59.0%).

After further subdivision of the total-nonfrail and frail subgroups by ISS stage (I/II vs. III), the PFS benefit of D-VMP versus VMP was also maintained in all subgroups (Figure 3A-B). The 36-month OS rate was higher with D-VMP versus VMP in all frailty subgroups (total-nonfrail + ISS I/II, 88.9% vs. 78.4%; total-nonfrail + ISS III, 71.7% vs. 66.3%; frail + ISS I/II, 75.2% vs. 63.7%, respectively; frail + ISS III, 67.8% vs. 52.3%; Figure 3C-D). In both total-nonfrail and frail patients, median OS was only reached with VMP in patients with ISS stage III disease.

The ORRs were higher with D-VMP versus VMP across frailty subgroups, with the total-nonfrail subgroup achieving higher ORRs than the frail subgroup in each treatment cohort (fit, 95.8% vs. 79.7%, $P = .0125$; intermediate, 92.1% vs. 72.3%, $P < .0001$; total-nonfrail, 93.0% vs. 75.0%, $P < .0001$; frail, 88.3% vs. 72.4%, $P = .0003$; Table 3). Deeper responses were observed with D-VMP versus VMP, including improved rates ≥CR and MRD-negativity (10^{-5} sensitivity threshold). See Supplementary Table 4 for a complete summary of response rates.

Safety

The most common (≥10% of patients) grade 3/4 treatment-emergent adverse events (TEAEs) are shown in Table 4 (see Supplementary Table 5 for all grade 3/4 TEAEs observed in >1 patient in either treatment cohort within each frailty subgroup). The 2 most common grade 3/4 TEAEs in all frailty subgroups with D-VMP and VMP were neutropenia (fit, 56.3% and 47.3%, respectively; intermediate, 33.3% and 39.5%; total-nonfrail, 39.2% and 42.4%; frail, 41.3% and 34.4%) and thrombocytopenia (fit, 27.1% and 41.9%; intermediate, 34.8% and 34.1%; total-nonfrail, 32.8% and 36.9%; frail, 36.9% and 39.1%). Grade 3/4 peripheral sensory neuropathy rates were low in all frailty subgroups with D-VMP and VMP (fit, 2.1% and 2.7%, respectively; intermediate, 2.2% and 3.1%; total-nonfrail, 2.2% and 3.0%; frail, 0.6% and 5.3%; Supplementary Table 5).

Serious TEAEs occurred more frequently in frail patients with both D-VMP and VMP: fit, 29.2% and 25.7%, respectively; intermediate, 47.8% and 29.5%; total-nonfrail, 43.0% and 28.1%; frail, 53.8% and 39.7%. The most common serious TEAE with D-VMP and VMP was pneumonia (fit, 4.2% and 1.4%, respectively; intermediate, 14.5% and 4.7%; total-nonfrail, 11.8% and 3.4%; frail, 11.9% and 3.3%), except in frail patients in the VMP cohort, in whom the most frequently occurring serious TEAE was cardiac failure (fit 0 [D-VMP] and 1.4% [VMP]; intermediate, 0 and 0.8%; total-nonfrail, 0 and 1.0%; frail, 1.3% and 4.0%; Supplementary Table 6).

Treatment discontinuations due to any grade TEAEs in the safety population occurred more frequently in frail patients with D-VMP and VMP: 2.1% and 8.1% of fit patients, respectively; 6.5% and

Figure 2 OS in the (A) fit, intermediate, and frail subgroups and (B) total-nonfrail and frail subgroups. CI = confidence interval; D-VMP = daratumumab plus bortezomib/melphalan/prednisone; HR = hazard ratio; OS = overall survival; VMP = bortezomib/melphalan/prednisone.

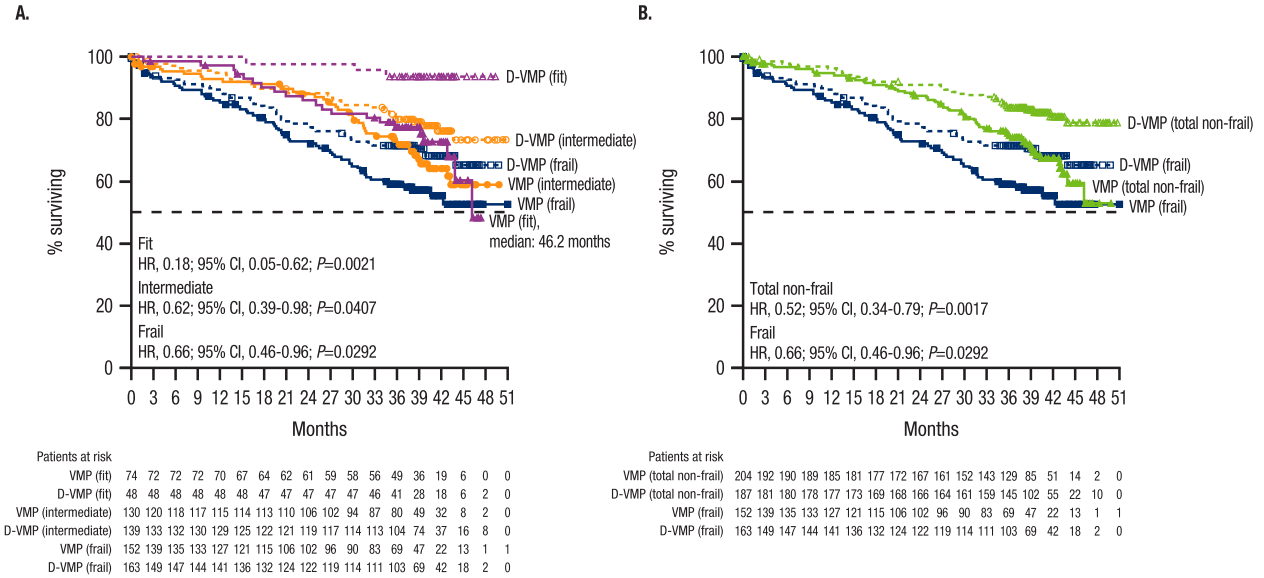


Figure 3 PFS subdivided by ISS stage in the (A) total-nonfrail and (B) frail subgroups; OS subdivided by ISS stage in the (C) total-nonfrail and (D) frail subgroups. CI = confidence interval; D-VMP = daratumumab plus bortezomib/melphalan/prednisone; HR = hazard ratio; ISS = International Staging System; OS = overall survival; PFS = progression-free survival; VMP = bortezomib/melphalan/prednisone.

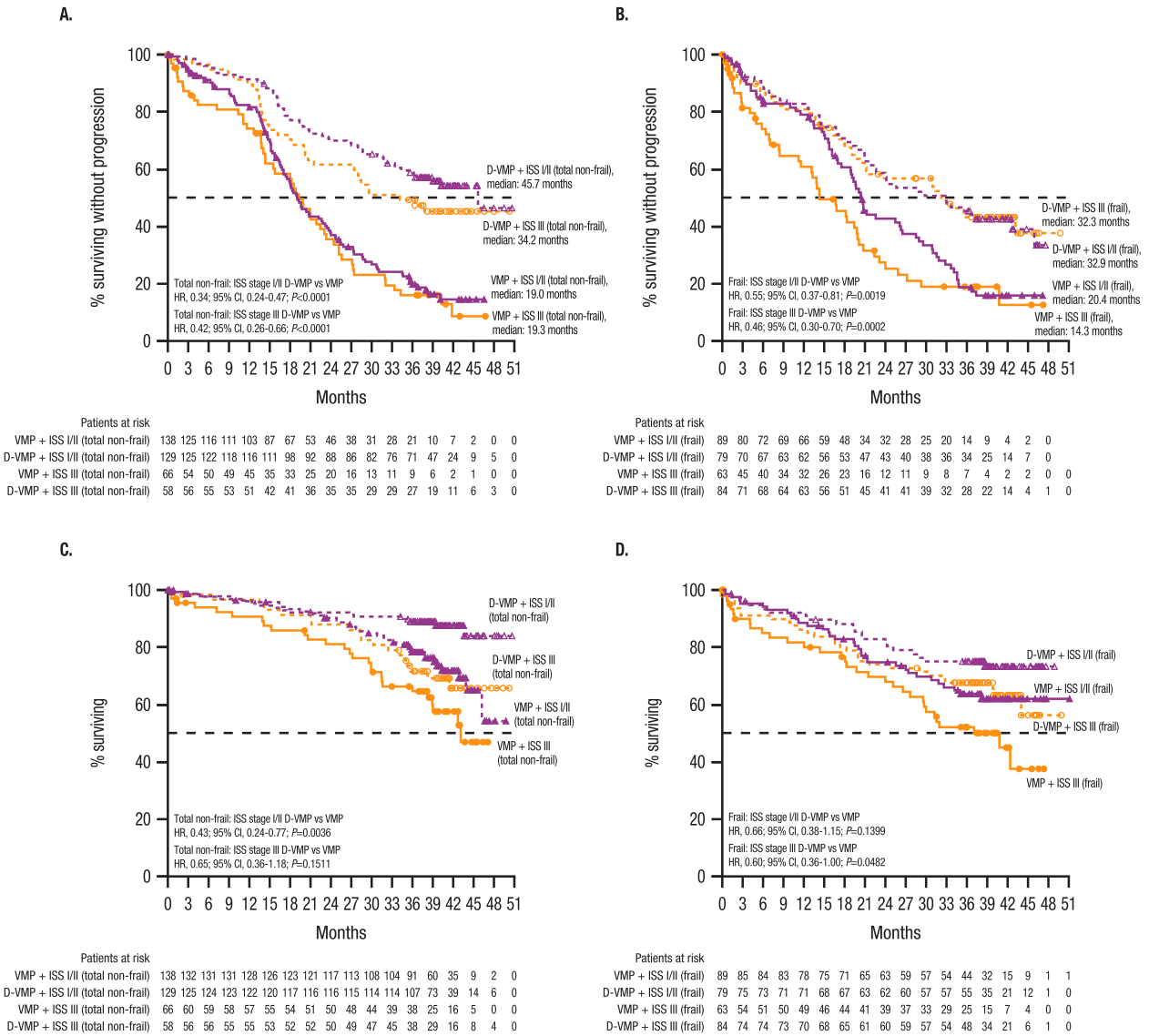


Table 3 Response and MRD-Negativity Rates (ITT Population)[a]

	Nonfrail[b]									Frail		
	Fit (17.3%;[c] *n* = 122/706)			Intermediate (38.1%;[c] *n* = 269/706)			Total-Nonfrail[b] (55.4%;[c] *n* = 391/706)			Frail (44.6%;[c] *n* = 315/706)		
	D-VMP (13.7%;[d] *n* = 48/350)	VMP (20.8%;[e] *n* = 74/356)	*P* Value	D-VMP (39.7%;[d] *n* = 139/350)	VMP (36.5%;[e] *n* = 130/356)	*P* Value	D-VMP (53.4%;[d] *n* = 187/350)	VMP (57.3%;[e] *n* = 204/356)	*P* Value	D-VMP (46.6%;[d] *n* = 163/350)	VMP (42.7%;[e] *n* = 152/356)	*P* Value
ORR, *n* (%)	46 (95.8)	59 (79.7)	.0125	128 (92.1)	94 (72.3)	<.0001	174 (93.0)	153 (75.0)	<.0001	144 (88.3)	110 (72.4)	.0003
≥CR	25 (52.1)	23 (31.1)	.0209	63 (45.3)	31 (23.8)	.0002	88 (47.1)	54 (26.5)	<.0001	72 (44.2)	36 (23.7)	.0001
≥VGPR	34 (70.8)	46 (62.2)	.3267	104 (74.8)	60 (46.2)	<.0001	138 (73.8)	106 (52.0)	<.0001	117 (71.8)	71 (46.7)	<.0001
MRD-negative (10^{-5}), *n* (%)	12 (25.0)	6 (8.1)	.0170	40 (28.8)	7 (5.4)	<.0001	52 (27.8)	13 (6.4)	<.0001	47 (28.8)	12 (7.9)	<.0001

Abbreviations: CR = complete response; D-VMP = daratumumab plus bortezomib/melphalan/prednisone; ITT = intent-to-treat; MRD = minimal residual disease; ORR = overall response rate; VMP = bortezomib/melphalan/prednisone; VGPR = very good partial response.
[a] Percentages in the table were calculated using the number of patients in each treatment cohort per frailty subgroup of the ITT population (fit: D-VMP, *n* = 48; VMP, *n* = 74; intermediate: D-VMP, *n* = 139; VMP, *n* = 130; total-nonfrail: D-VMP, *n* = 187; VMP, *n* = 204; frail: D-VMP, *n* = 163; VMP, *n* = 152) as the denominator, unless otherwise indicated.
[b] Nonfrail subgroup consists of fit and intermediate patients.
[c] Percentage was calculated using the number of patients in the ITT population as the denominator.
[d] Percentage was calculated using the number of patients in the D-VMP cohort of the ITT population as the denominator.
[e] Percentage was calculated using the number of patients in the VMP cohort of the ITT population as the denominator.

Table 4 Most Common Grade 3/4 TEAEs (≥10% of Patients) and TEAEs With Outcome of Death (>1 Patient; Safety Population)[a]

	Nonfrail[b]						Frail	
	Fit (17.4%;[c] *n* = 122/700)		Intermediate (38.1%;[c] *n* = 267/700)		Total-Nonfrail[b] (55.6%;[c] *n* = 389/700)		Frail (44.4%;[c] *n* = 311/700)	
	D-VMP (13.9%;[d] *n* = 48/346)	VMP (20.9%;[e] *n* = 74/354)	D-VMP (39.9%;[d] *n* = 138/346)	VMP (36.4%;[e] *n* = 129/354)	D-VMP (53.8%;[d] *n* = 186/346)	VMP (57.3%;[e] *n* = 203/354)	D-VMP (46.2%;[d] *n* = 160/346)	VMP (42.7%;[e] *n* = 151/354)
Total number of patients with grade 3/4 TEAE, *n* (%)	35 (72.9)	57 (77.0)	115 (83.3)	94 (72.9)	150 (80.6)	151 (74.4)	127 (79.4)	123 (81.5)
Hematologic, *n* (%)								
Neutropenia	27 (56.3)	35 (47.3)	46 (33.3)	51 (39.5)	73 (39.2)	86 (42.4)	66 (41.3)	52 (34.4)
Thrombocytopenia	13 (27.1)	31 (41.9)	48 (34.8)	44 (34.1)	61 (32.8)	75 (36.9)	59 (36.9)	59 (39.1)
Lymphopenia	6 (12.5)	2 (2.7)	7 (5.1)	7 (5.4)	13 (7.0)	9 (4.4)	14 (8.8)	13 (8.6)
Anemia	5 (10.4)	14 (18.9)	21 (15.2)	24 (18.6)	26 (14.0)	38 (18.7)	34 (21.3)	32 (21.2)
Leukopenia	5 (10.4)	4 (5.4)	10 (7.2)	8 (6.2)	15 (8.1)	12 (5.9)	13 (8.1)	18 (11.9)
Nonhematologic, *n* (%)								
Infections	6 (12.5)	11 (14.9)	38 (27.5)	15 (11.6)	44 (23.7)	26 (12.8)	48 (30.0)	27 (17.9)
Pneumonia	2 (4.2)	1 (1.4)	20 (14.5)	6 (4.7)	22 (11.8)	7 (3.4)	23 (14.4)	8 (5.3)
Total number of patients with a TEAE with outcome of death, *n* (%)	0	2 (2.7)	7 (5.1)	5 (3.9)	7 (3.8)	7 (3.4)	17 (10.6)	13 (8.6)
Cardiac arrest	0	0	1 (0.7)	0	1 (0.5)	0	0	2 (1.3)
Death	0	0	0	0	0	0	2 (1.3)	2 (1.3)
Pneumonia	0	0	0	0	0	0	2 (1.3)	0

Abbreviations: D-VMP = daratumumab plus bortezomib/melphalan/prednisone; TEAE = treatment-emergent adverse event; VMP = bortezomib/melphalan/prednisone.
[a] Percentages in the table were calculated using the number of patients in each treatment cohort per frailty subgroup of the safety population (fit: D-VMP, *n* = 48; VMP, *n* = 74; intermediate: D-VMP, *n* = 138; VMP, *n* = 129; total-nonfrail: D-VMP, *n* = 186; VMP, *n* = 203; frail: D-VMP, *n* = 160; VMP, *n* = 151) as the denominator, unless otherwise indicated.
[b] Nonfrail subgroup consists of fit and intermediate patients.
[c] Percentage was calculated using the number of patients in the safety population as the denominator.
[d] Percentage was calculated using the number of patients in the D-VMP cohort of the safety population as the denominator.
[e] Percentage was calculated using the number of patients in the VMP cohort of the safety population as the denominator.

6.2% of intermediate patients; 5.4% and 6.9% of total-nonfrail patients; and 8.8% and 12.6% of frail patients (Supplementary Table 7). The most common TEAE that led to discontinuations in >1 patient was pneumonia with D-VMP (2 patients in the intermediate subgroup and 1 patient in the frail subgroup; VMP, 1 patient in the frail subgroup) and was peripheral sensory neuropathy with VMP (1 patient each in the fit and intermediate subgroups and 4 patients in the frail subgroup; D-VMP, 0 patients). Pneumonia was the most frequently reported infection leading to discontinuations.

Deaths due to any cause and TEAEs resulting in death occurred more frequently in frail patients treated with either D-VMP or VMP. Deaths occurred in 19.7% of fit patients (D-VMP, 3 [6.3%]; VMP, 21 [28.4%]), 27.3% of intermediate patients (31 [22.5%]; 42 [32.6%]), 24.9% of total-nonfrail patients (34 [18.3%]; 63 [31.0%]), and 36.0% of frail patients (49 [30.6%]; 63 [41.7%]). TEAEs resulting in death are summarized in Table 4. Disease progression as the primary cause of death occurred in 9.0% of fit patients (D-VMP, 2 [4.2%]; VMP, 9 [12.2%]), 13.9% of intermediate patients (18 [13.0%]; 19 [14.7%]), 12.3% of total-nonfrail patients (20 [10.8%]; 28 [13.8%]), and 13.5% of frail patients (17 [10.6%]; 25 [16.6%]). Adverse events as the primary cause of death occurred in 1.6% of fit patients (D-VMP, 0; VMP, 2 [2.7%]), 5.2% of intermediate patients (8 [5.8%]; 6 [4.7%]), 4.1% of total-nonfrail patients (8 [4.3%]; 8 [3.9%]), and 10.9% of frail patients (21 [13.1%]; 13 [8.6%]).

Discussion

After >3 years of follow-up, D-VMP maintained improved efficacy versus VMP in transplant-ineligible NDMM patients, regardless of frailty status. When comparing frail to total-nonfrail subgroups, the frail subgroup generally had slightly poorer outcomes in both treatment cohorts for PFS and OS. However, D-VMP reduced the risk of disease progression or death by 64% in total-nonfrail patients and by 49% in frail patients. The median PFS with D-VMP in total-nonfrail (45.7 months) and frail (32.9 months) patients was longer than that observed with continuous lenalidomide and dexamethasone in total-nonfrail (31.3 months) and frail (19.4 months) patients in the FIRST trial, which had a similar patient population to that in ALCYONE.[19] Additionally, D-VMP reduced the risk of death by 48% in total-nonfrail patients and by 34% in frail patients. Regardless of frailty status, deep responses were achieved with D-VMP versus VMP, with improved ≥CR and MRD-negativity rates. These results suggest daratumumab induces deep responses even among those who are more likely to require bortezomib dose reductions (32.5% of frail patients in the D-VMP cohort), possibly reflecting the ability of frail patients to tolerate and continue treatment.

Facon et al. demonstrated that further subdivision of both the frail and nonfrail subgroups by ISS disease stage (I/II vs. III) resulted in improved prognostic value of their frailty scale, as was previously observed with the IMWG frailty scale.[19,20] In our study, the greater PFS benefit of D-VMP versus VMP was also seen in both total-nonfrail and frail patients, regardless of ISS disease stage category (I/II and III), with the total-nonfrail + ISS I/II subgroup achieving the longest median PFS with D-VMP. Similarly, a greater OS benefit of D-VMP versus VMP was observed in both total-nonfrail and frail patients in both ISS disease stage categories. Median OS was not reached with D-VMP in either frailty subgroup, regardless of ISS stage, whereas median OS was reached with VMP in total-nonfrail and frail patients with ISS stage III disease. These observations demonstrate that even in the sickest patients—frail patients in the higher ISS disease stage category—D-VMP provides a PFS and OS benefit versus VMP.

The safety profile of D-VMP in all frailty subgroups was generally consistent with the overall population of ALCYONE.[10] Grade 3/4 pneumonia was more frequent in patients who received D-VMP and was also the most common serious TEAE among D-VMP–treated patients. Compared with total-nonfrail patients, frail patients had an increased incidence of serious TEAEs and deaths in both treatment cohorts. Although grade 3/4 neutropenia was more common in fit patients, fit patients had a longer duration of treatment and fewer treatment discontinuations. Grade 3/4 neutropenia was more frequent in frail patients who received D-VMP, while the incidence of neutropenia was comparable between D-VMP and VMP in total-nonfrail patients. During Cycles 1 to 9, a lower proportion of patients in the D-VMP cohort discontinued treatment versus the VMP cohort across frailty subgroups. This observation may have been due to a greater likelihood of investigators managing AEs by treatment discontinuation in VMP–treated versus D-VMP–treated patients and instead by cycle delay or dose modification in D-VMP-treated versus VMP-treated patients. The most common TEAE that led to treatment discontinuations was pneumonia in the D-VMP cohort and peripheral sensory neuropathy in the VMP cohort. However, rates of grade 3/4 peripheral sensory neuropathy were low in both treatment cohorts across frailty subgroups, no patients in the D-VMP cohort discontinued treatment due to peripheral sensory neuropathy, and the percentages of patients in the VMP cohort who discontinued treatment due to this TEAE were low across frailty subgroups. The low rates of treatment discontinuations due to peripheral sensory neuropathy may be attributed to the use of a once-weekly bortezomib dosing schedule during Cycles 2 to 9. Bringhen et al. previously demonstrated that once-weekly bortezomib provided similar efficacy to twice-weekly bortezomib in transplant-ineligible NDMM patients with improved safety, including a significantly lower rate of treatment discontinuations due to peripheral neuropathy.[24]

Given the similar patient populations between the FIRST trial and ALCYONE, and the availability of data needed for retrospective frailty score calculation, the frailty scale used in the frailty subgroup analysis of the FIRST trial was selected for our frailty subgroup analysis of ALCYONE.[19] Our study provides validity for the frailty scale used in the FIRST trial analysis,[19] in which, as in the current study, the use of the scale predicted clinical outcomes in transplant-ineligible NDMM patients. With the emergence of new treatment regimens for multiple myeloma,[25] further use of this frailty scale in clinical trials may help optimize treatment strategies based on patient frailty status. A recent position paper by the European Myeloma Network emphasized the need for the development of validated frailty scales that can be used to maximize treatment benefit while minimizing toxicity in multiple myeloma.[22] These data also complement the ALCYONE age subgroup analysis.[26] Therefore, D-VMP is a key first-line regimen

to consider in NDMM patients ineligible for autologous stem cell transplantation.

These results add to those of a frailty subgroup analysis of the phase 3 MAIA study of daratumumab plus lenalidomide/dexamethasone (D-Rd) versus lenalidomide/dexamethasone (Rd) alone in transplant-ineligible NDMM patients; frailty assessments were performed using the same scale used in our study.[27] After a median follow-up of 36.4 months, the PFS benefit of D-Rd over Rd was maintained in all frailty subgroups.[27] OS was not mature at the time of the analysis. In ALCYONE, OS benefit of D-VMP versus VMP was observed in all frailty subgroups despite frailty being a strong predictor of shorter OS.[20] Patients in ALCYONE received single-agent daratumumab during Cycles 10+, which likely resulted in the better safety profile of frail daratumumab-treated patients in this study compared with in MAIA.[27] The treatment strategy of switching to single-agent daratumumab for maintenance may be more suitable for frail patients. Together, the frailty subgroup analyses of ALCYONE and MAIA support the use of daratumumab-containing regimens in transplant-ineligible NDMM patients.

One limitation of this study was the retrospective assessment of frailty score. Notably, the CCI was calculated retrospectively based on reported medical history (collected and monitored per protocol) that may contain missing data, leading to a potential underestimation or overestimation of patients in each frailty subgroup. Additionally, although 44.6% of patients in the overall population were categorized as frail, frail patients in this study may not be representative of real-world frail patients; patients with an ECOG PS score ≥3 were excluded from ALCYONE, along with patients with comorbidities that may interfere with the study procedures. The strict inclusion and exclusion criteria of phase 3 clinical trials limit the ability of these results to be generalized to more frail patients seen in clinical practice.

Conclusion

Improved efficacy with D-VMP versus VMP was observed across frailty subgroups, with no new safety concerns. Our findings, although based on a retrospective assessment of frailty, support the clinical benefit of D-VMP in transplant-ineligible NDMM patients enrolled in ALCYONE, regardless of frailty status.

Clinical Practice Points

- Daratumumab is approved in many countries as monotherapy and in combination with standard-of-care regimens for multiple myeloma.
- In the primary analysis of the phase 3 ALCYONE study (16.5-month median follow-up), daratumumab plus bortezomib/melphalan/prednisone (D-VMP) significantly prolonged progression-free survival (PFS) over bortezomib/melphalan/prednisone (VMP) in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients.
- In the updated analysis of ALCYONE (40.1-month median follow-up), D-VMP continued to show significant PFS benefit and significantly prolonged overall survival (OS), even in patients aged ≥75 years.
- Although D-VMP improved outcomes in older patients, such patients often vary widely in fitness level; therefore, we conducted a subgroup analysis of ALCYONE based on frailty status instead of based solely on age.
- Frailty assessment was performed retrospectively on all patients using age, Charlson comorbidity index, and baseline Eastern Cooperative Oncology Group performance status score.
- After >3 years of follow-up, D-VMP maintained improved efficacy versus VMP in transplant-ineligible NDMM patients, regardless of frailty status.
- D-VMP reduced the risk of disease progression or death by 64% in total-nonfrail patients and by 49% in frail patients.
- Additionally, D-VMP reduced the risk of death by 48% in total-nonfrail patients and by 34% in frail patients.
- Deep responses were achieved with D-VMP versus VMP across frailty subgroups.
- The safety profile of D-VMP in frailty subgroups was generally consistent with that for the overall population of ALCYONE.
- Our findings, although based on a retrospective assessment of frailty, support the clinical benefit of D-VMP in transplant-ineligible NDMM patients enrolled in ALCYONE, regardless of frailty status.

Data Sharing 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 Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Authors' Contributions

All authors contributed to the conception and design of the study or to the acquisition, analysis, or interpretation of the data. All authors drafted the article, revised the article critically for important intellectual content, approved the final version for publication, and agree to be accountable for all aspects of the work.

Disclosure

M.-V.M. received honoraria and served as a consultant or in an advisory role for Amgen, GlaxoSmithKline, Celgene, Janssen, Takeda, Seattle Genetics, Adaptive, and AbbVie. M.A.D. received honoraria from Janssen, Celgene, Takeda, Amgen, and Bristol Myers Squibb; and served as a consultant or in an advisory role for Janssen, Celgene, Takeda, Amgen, and Bristol Myers Squibb. M.C. received honoraria from AbbVie, GlaxoSmithKline, Bristol Myers Squibb, Adaptive Biotechnologies, Takeda, Janssen, and Celgene. S.K. received honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen, and Takeda; served as a consultant or in an advisory role for Amgen, Bristol Myers Squibb, Celgene, Janssen, and Takeda; and received research funding from Amgen, Bristol Myers Squibb, Celgene, Janssen, and Takeda. C.D. served as a consultant or in an advisory role for Janssen. P.L. served as a consultant or in an advisory role for Janssen, Amgen, Celgene, and Takeda. A.M.L. received honoraria from Novartis, Janssen, AbbVie, Gilead, Roche,

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2021.06.005.

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