The 7th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

Daratumumab Plus Bortezomib, Melphalan, and Prednisone (D-VMP) Versus Bortezomib, Melphalan, and Prednisone (VMP) in Newly Diagnosed Multiple Myeloma (NDMM) Patients Ineligible for Transplantation: Frailty Subgroup Analysis of ALCYONE

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INTRODUCTION

- 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[1]
- 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[2]
- However, older patients vary in fitness levels,[3,4] and frail patients will often have a reduced tolerance to cancer treatment regimens and increased symptom burden[4,5]
- We present a subgroup analysis of patients in ALCYONE comparing D-VMP versus VMP by frailty status
  - Frailty scores were calculated retrospectively for all patients using age, Charlson Comorbidity Index (based on a retrospective review of each patient's medical history), and baseline Eastern Cooperative Oncology Group performance status score[3]
  - Sum of scores classified patients as fit (0), intermediate (1), or frail (≥2); fit or intermediate patients were considered non-frail

RESULTS

- Among randomised patients (D-VMP, n = 350; VMP, n = 356), 391 (55.4%) were non-frail (D-VMP, 187 [53.4%]; VMP, 204 [57.3%]) and 315 (44.6%) were frail (D-VMP, 163 [46.6%]; VMP, 152 [42.7%])
- Demographic and baseline characteristics were generally balanced between the treatment cohorts within each frailty subgroup (**Table 1**)

Table 1. Demographic and Baseline Characteristics

	Non-frail[a]						Frail	
	Fit (n = 122)		Intermediate (n = 269)		Total non-frail[a] (n = 391)		Frail (n = 315)	
	D-VMP (n = 48)	VMP (n = 74)	D-VMP (n = 139)	VMP (n = 130)	D-VMP (n = 187)	VMP (n = 204)	D-VMP (n = 163)	VMP (n = 152)
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)
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 (%)[b]								
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)
CrCl, n (%)								
≥90 mL/min	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 mL/min	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 mL/min	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 mL/min	0	0	1 (0.7)	2 (1.5)	1 (0.5)	2 (1.0)	2 (1.2)	6 (3.9)
Cytogenetic profile, n (%)[c]								
N	45	63	125	108	170	171	144	131
Standard risk	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[d]	7 (15.6)	9 (14.3)	13 (10.4)	18 (16.7)	20 (11.8)	27 (15.8)	33 (22.9)	18 (13.7)

D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.
[a]Total non-frail subgroup consists of fit and intermediate patients.
[b]Based on the combination of serum β2-microglobulin and albumin.
[c]Cytogenetic risk was based on fluorescence in situ hybridisation 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.
[d]Patients with high cytogenetic risk had a del17p, t(4;14), or t(14;16) abnormality.

- Patient disposition during Cycles 1 to 9 is summarised by frailty status in **Table 2**
  - The 2 most common reasons for treatment discontinuation in all frailty subgroups were progressive disease and adverse events

Table 2. Patient Disposition During Cycles 1 to 9 (Safety Population)

	Total non-frail[a] (n = 389)		Frail (n = 311)	
	D-VMP (n = 186)	VMP (n = 203)	D-VMP (n = 160)	VMP (n = 151)
Patients who discontinued treatment, n (%)	22 (11.8)	55 (27.1)	46 (28.8)	63 (41.7)
Reason for discontinuation, n (%)				
Progressive disease	9 (4.8)	25 (12.3)	14 (8.8)	22 (14.6)
Adverse event	7 (3.8)	14 (6.9)	11 (6.9)	20 (13.2)
Noncompliance with study drug[b]	1 (0.5)	3 (1.5)	9 (5.6)	12 (7.9)
Death	2 (1.1)	4 (2.0)	9 (5.6)	4 (2.6)
Physician decision	0	4 (2.0)	0	3 (2.0)
Patient withdrawal	2 (1.1)	5 (2.5)	0	1 (0.7)
Other	1 (0.5)	0	3 (1.9)	1 (0.7)

D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.
[a]Total non-frail subgroup consists of fit and intermediate patients.
[b]Based on reason "Patient refused further study treatment."

- The median relative dose intensity of daratumumab was similar across frailty subgroups, and the median relative dose intensities of bortezomib, melphalan, and prednisone-equivalent were similar across frailty subgroups and between D-VMP versus VMP in all frailty subgroups (**Table 3**)

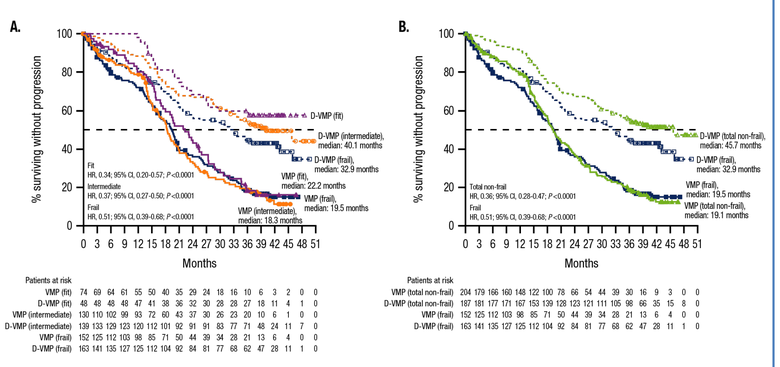
Table 3. Summary of RDI (Safety Population)

	Total non-frail[a] (n = 389)		Frail (n = 311)	
	D-VMP (n = 186)	VMP (n = 203)	D-VMP (n = 160)	VMP (n = 151)
Bortezomib RDI, %				
N	186	203	159	151
Median (range)	95.7 (33.8-103.6)	95.1 (36.2-105.8)	95.3 (12.1-106.3)	92.7 (26.2-110.6)
Melphalan RDI, %				
N	185	203	159	150
Median (range)	97.4 (57.9-142.5)	97.1 (37.2-119.6)	95.9 (25.0-136.9)	95.4 (44.4-107.8)
Prednisone-equivalent RDI, %				
N	186	203	160	150
Median (range)	99.1 (24.4-110.0)	98.8 (35.3-106.5)	99.0 (30.1-129.8)	98.9 (53.7-106.3)
Daratumumab RDI, %				
N	186	–	160	–
Median (range)	99.3 (6.9-106.2)	–	98.5 (1.3-105.9)	–

D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; RDI, relative dose intensity.
[a]Total non-frail subgroup consists of fit and intermediate patients.

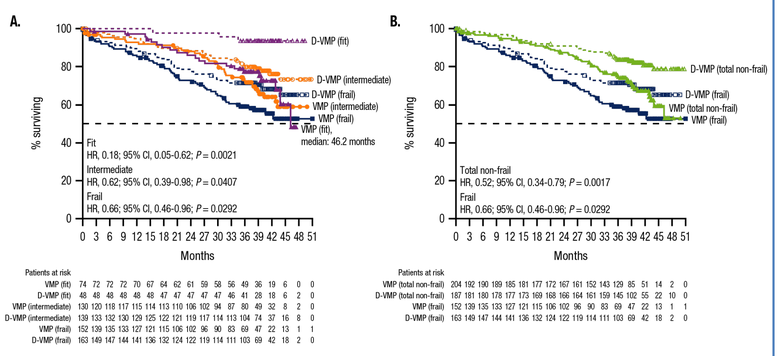
- After a median follow-up of 40.1 months, the PFS benefit of D-VMP versus VMP was maintained in all frailty subgroups (**Figures 1A** and **1B**)
- The OS benefit of D-VMP versus VMP was also maintained in all frailty subgroups (**Figures 2A** and **2B**)

Figure 1. PFS in the (A) fit, intermediate, and frail subgroups and (B) total non-frail and frail subgroups.



PFS, progression-free survival; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; HR, hazard ratio; CI, confidence interval.

Figure 2. OS in the (A) fit, intermediate, and frail subgroups and (B) total non-frail and frail subgroups.



OS, overall survival; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; HR, hazard ratio; CI, confidence interval.

- The overall response rates (ORRs) were higher with D-VMP versus VMP across frailty subgroups, with the total non-frail subgroup achieving higher ORRs than the frail subgroup in each treatment cohort (**Table 4**)
  - Deeper responses were observed with D-VMP versus VMP, including improved rates of ≥complete response and minimal residual disease (MRD)–negativity (10^{-5} sensitivity threshold)

Table 4. Response and MRD-negativity Rates (ITT Population)

	Total non-frail[a] (n = 391)			Frail (n = 315)		
	D-VMP (n = 187)	VMP (n = 204)	*P* value	D-VMP (n = 163)	VMP (n = 152)	*P* value
ORR, n (%)	174 (93.0)	153 (75.0)	<0.0001	144 (88.3)	110 (72.4)	0.0003
≥CR	88 (47.1)	54 (26.5)	<0.0001	72 (44.2)	36 (23.7)	0.0001
sCR	49 (26.2)	13 (6.4)	<0.0001	32 (19.6)	15 (9.9)	0.0152
CR	39 (20.9)	41 (20.1)		40 (24.5)	21 (13.8)	
≥VGPR	138 (73.8)	106 (52.0)	<0.0001	117 (71.8)	71 (46.7)	<0.0001
VGPR	50 (26.7)	52 (25.5)		45 (27.6)	35 (23.0)	
PR	36 (19.3)	47 (23.0)		27 (16.6)	39 (25.7)	
SD, n (%)	9 (4.8)	41 (20.1)		11 (6.7)	35 (23.0)	
PD, n (%)	0	1 (0.5)		0	1 (0.7)	
NE, n (%)	4 (2.1)	9 (4.4)		8 (4.9)	6 (3.9)	
MRD-negative (10^{-5}), n (%)	52 (27.8)	13 (6.4)	<0.0001	47 (28.8)	12 (7.9)	<0.0001

MRD, minimal residual disease; ITT, intent-to-treat; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.
[a]Total non-frail subgroup consists of fit and intermediate patients.

- The most common (≥10% patients) grade 3/4 treatment-emergent adverse events (TEAEs) are shown in **Table 5**; the 2 most common grade 3/4 TEAEs in all frailty subgroups with D-VMP and VMP were neutropaenia and thrombocytopaenia

Table 5. Most Common Grade 3/4 TEAEs (≥10% of Patients) and TEAEs With an Outcome of Death (Safety Population)

	Total non-frail[a] (n = 389)		Frail (n = 311)	
	D-VMP (n = 186)	VMP (n = 203)	D-VMP (n = 160)	VMP (n = 151)
Total number of patients with grade 3/4 TEAE, n (%)	150 (80.6)	151 (74.4)	127 (79.4)	123 (81.5)
Haematologic, n (%)				
Neutropaenia	73 (39.2)	86 (42.4)	66 (41.3)	52 (34.4)
Thrombocytopaenia	61 (32.8)	75 (36.9)	59 (36.9)	59 (39.1)
Anaemia	26 (14.0)	38 (18.7)	34 (21.3)	32 (21.2)
Leukopaenia	15 (8.1)	12 (5.9)	13 (8.1)	18 (11.9)
Lymphopaenia	13 (7.0)	9 (4.4)	14 (8.8)	13 (8.6)
Nonhaematologic, n (%)				
Infections	44 (23.7)	26 (12.8)	48 (30.0)	27 (17.9)
Pneumonia	22 (11.8)	7 (3.4)	23 (14.4)	8 (5.3)
Total number of patients with a TEAE with an outcome of death, n (%)	7 (3.8)	7 (3.4)	17 (10.6)	13 (8.6)
Cardiac arrest	1 (0.5)	0	0	2 (1.3)
Death	0	0	2 (1.3)	2 (1.3)
Pneumonia	0	0	2 (1.3)	0

TEAE, treatment-emergent adverse event; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.
[a]Total non-frail subgroup consists of fit and intermediate patients.

- Treatment discontinuations due to any grade TEAEs in the safety population occurred more frequently in frail patients with D-VMP and VMP (**Table 6**)

Table 6. Most Common TEAEs Leading to Treatment Discontinuation (>1 Patient; Safety Population)

	Total non-frail[a] (n = 389)		Frail (n = 311)	
	D-VMP (n = 186)	VMP (n = 203)	D-VMP (n = 160)	VMP (n = 151)
Total number of patients with a TEAE leading to treatment discontinuation, n (%)	10 (5.4)	14 (6.9)	14 (8.8)	19 (12.6)
Nonhaematologic, n (%)				
Fatigue	0	0	1 (0.6)	2 (1.3)
Peripheral sensory neuropathy	0	2 (1.0)	0	4 (2.6)
Infections	4 (2.2)	3 (1.5)	2 (1.3)	3 (2.0)
Pneumonia	2 (1.1)	0	1 (0.6)	1 (0.7)

TEAE, treatment-emergent adverse event; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.
[a]Total non-frail subgroup consists of fit and intermediate patients.

CONCLUSIONS

- 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 non-frail patients and by 49% in frail patients
- Regardless of frailty status, deep responses were achieved with D-VMP versus VMP, with improved ≥complete response and MRD-negativity rates
- The safety profile of D-VMP in all frailty subgroups was generally consistent with the overall population of ALCYONE[1]
- 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

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ACKNOWLEDGEMENTS

The authors thank the patients who participated in this study and their families, as well as the study co-investigators, research nurses, and coordinators at each of the clinical sites.

This study (ClinicalTrials.gov Identifier: NCT02195479) was sponsored by Janssen Research & Development, LLC. Medical writing and editorial support were provided by Melissa Brunckhorst, PhD, of Cello Health Communications/MedErgy, and were funded by Janssen Global Services, LLC.

DISCLOSURES

M-VM received honoraria and served as a consultant or in an advisory role for Amgen, GlaxoSmithKline, Celgene, Janssen, Takeda, Seattle Genetics, Adaptive, and AbbVie. MAD 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. MC received honoraria from AbbVie, GlaxoSmithKline, Bristol Myers Squibb, Adaptive Biotechnologies, Takeda, Janssen, and Celgene. SK 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. CD served as a consultant or in an advisory role for Janssen. PL served as a consultant or in an advisory role for Janssen, Amgen, Celgene, and Takeda. AML received honoraria from Novartis, Janssen, AbbVie, Gilead, Roche, Amgen, AstraZeneca, Mundipharma, Celgene, Takeda, Servier, and Incyte. S-SY served as a consultant or in an advisory role for Amgen, Astellas, Celgene, Janssen, Novartis, and Takeda; received honoraria from Novartis; and received research funding from Kyowa Kirin, Roche-Genentech, and Yuhan Pharmaceuticals. MG served as a consultant or in an advisory role for and received travel support from Celgene, Janssen, Takeda, Amgen, and Novartis. SI received honoraria from Janssen, Celgene, Takeda, ONO, Bristol Myers Squibb, Daiichi Sankyo, and Sanofi; and received research grants from Janssen, Celgene, Takeda, ONO, Bristol Myers Squibb, Daiichi Sankyo, Sanofi, Merck Sharp & Dohme, Gilead Sciences, AbbVie, Chugai, and Kyowa Kirin. JB received honoraria from Janssen, Celgene, Amgen, and Takeda. RC and RVR are employees of Janssen. HP and SW are employees of Janssen and own Johnson and Johnson stock. JS-M served in a consulting or advisory role for Amgen, Bristol Myers Squibb, Celgene, Janssen, Merck Sharp & Dohme, Novartis, Takeda, Sanofi, Roche, AbbVie, GlaxoSmithKline, and Karyopharm. KS, ZN, LP, SG, AC, PC, GI, and TF have nothing to disclose.

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