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Daratumumab Plus Bortezomib-Melphalan-Prednisone (VMP) in Elderly (≥75 y) Patients (Pts) With Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplantation (ALCYONE)

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INTRODUCTION

- Patients with newly diagnosed multiple myeloma (NDMM) who are ≥70 years of age or have significant comorbidities are usually ineligible for autologous stem cell transplantation (ASCT)[1]
- Outside of the United States, bortezomib, melphalan, and prednisone (VMP) is a standard of care for these patients based on the VISTA,[2,3] PETHEMA/GEM2005MAS65,[4] and GIMEMA[5] studies
- Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action[6]
- Daratumumab is approved in many countries as a monotherapy for heavily pretreated patients with relapsed or refractory multiple myeloma (RRMM) and in combination with standard-of-care regimens in patients with RRMM who have received ≥1 prior therapy[7]
- Daratumumab in combination with VMP (D-VMP) has recently been approved in Brazil and the United States for NDMM patients who are ineligible for ASCT[8]
- In patients with NDMM who are ineligible for ASCT, D-VMP prolonged progression-free survival (PFS) compared with VMP and was well tolerated in the phase 3 ALCYONE study (ClinicalTrials.gov Identifier: NCT02195479)[9]
- We report the efficacy and safety data of elderly (≥75 years) and non-elderly (<75 years) NDMM patients in ALCYONE

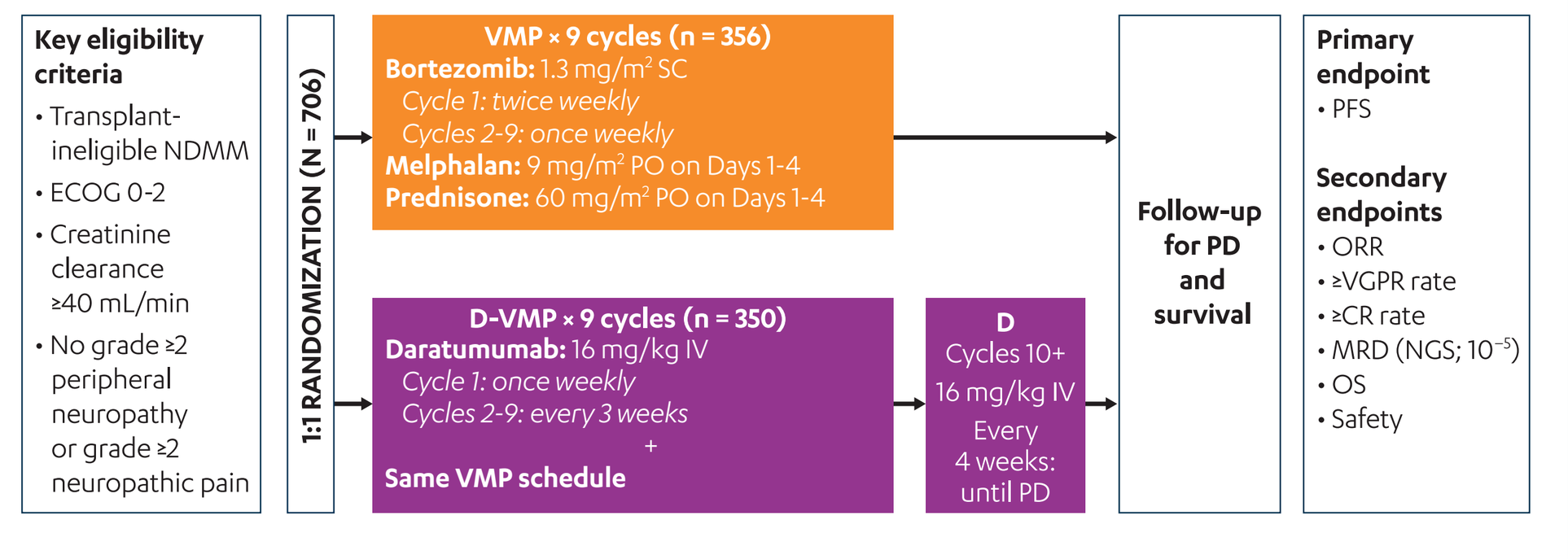
METHODS

Patients

- Eligible patients had NDMM and were ≥65 years of age or otherwise ineligible for high-dose chemotherapy and ASCT
- Patients were excluded for the following:
  - Hemoglobin <7.5 g/dL
  - Neutrophils <1.0 × 10⁹/L
  - Platelets <70 × 10⁹/L
  - Aspartate aminotransferase and alanine aminotransferase ≥2.5 times the upper limit of normal
  - Creatinine clearance <40 mL/min
  - Primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering MM, or Waldenström's macroglobulinemia
  - Previous systemic therapy or ASCT
  - Grade ≥2 peripheral neuropathy or grade ≥2 neuropathic pain

Study Design and Treatment

- ALCYONE is a randomized phase 3 study of D-VMP versus VMP in transplant-ineligible patients with NDMM (**Figure 1**)
- All patients received up to nine 6-week cycles of VMP (bortezomib 1.3 mg/m² subcutaneously on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1 and Days 1, 8, 22, and 29 of Cycles 2-9; melphalan 9 mg/m² orally and prednisone 60 mg/m² orally on Days 1-4 of each cycle)
- Patients in the D-VMP group also received daratumumab 16 mg/kg intravenously every week in Cycle 1, every 3 weeks in Cycles 2-9, and every 4 weeks in Cycles 10+ (post VMP-treatment phase) until disease progression
  - Cycles 1-9: 6-week cycles
  - Cycles 10+: 4-week cycles
- Stratification factors were International Staging System (I vs II vs III), region (Europe vs other), and age (<75 vs ≥75 years)



Key eligibility criteria
• Transplant-ineligible NDMM
• ECOG 0-2
• Creatinine clearance ≥40 mL/min
• No grade ≥2 peripheral neuropathy or grade ≥2 neuropathic pain
1:1 RANDOMIZATION (N = 706)
VMP × 9 cycles (n = 356)
Bortezomib: 1.3 mg/m² SC
Cycle 1: twice weekly
Cycles 2-9: once weekly
Melphalan: 9 mg/m² PO on Days 1-4
Prednisone: 60 mg/m² PO on Days 1-4
D-VMP × 9 cycles (n = 350)
Daratumumab: 16 mg/kg IV
Cycle 1: once weekly
Cycles 2-9: every 3 weeks
+
Same VMP schedule
D
Cycles 10+
16 mg/kg IV
Every 4 weeks: until PD
Follow-up for PD and survival
Primary endpoint
• PFS
Secondary endpoints
• ORR
• ≥VGPR rate
• ≥CR rate
• MRD (NGS; 10⁻⁵)
• OS
• Safety

NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; VMP, bortezomib/melphalan/prednisone; SC, subcutaneously; PO, orally; D-VMP, daratumumab/bortezomib/melphalan/prednisone; IV, intravenously; D, daratumumab; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.

Figure 1. ALCYONE study design.

Statistical Analyses and Assessments

- PFS, overall response rate (ORR), rate of very good partial response (VGPR) or better, rate of complete response (CR) or better, and minimal residual disease (MRD)–negativity rate were sequentially tested
  - Time to event variables were evaluated using the Kaplan-Meier method
  - Response rates were assessed with a stratified Cochran-Mantel-Haenszel test
- A total of 360 PFS events was estimated to provide 85% power to detect an 8-month PFS improvement over a 21-month median PFS for VMP; interim analysis was planned when 216 events of disease progression or death occurred
- MRD-negativity rate (10^{-5} threshold) was evaluated in the intent-to-treat (ITT) population via next-generation sequencing using clonoSEQ® assay V2.0 (Adaptive Biotechnologies, Seattle, WA, USA)

RESULTS

Patients and Treatments

- The median duration of follow-up was 16.5 months
- Among the 706 patients enrolled in the study (350 D-VMP; 356 VMP), 211 were aged ≥75 years and 495 were aged <75 years (**Table 1**)
- The median duration of study treatment was 14.5 months for D-VMP versus 12.0 months for VMP among patients ≥75 years of age and 15.0 months for D-VMP versus 12.0 months for VMP among patients <75 years of age
- The median cumulative dose of bortezomib was 43.1 mg/m² and 34.1 mg/m² with D-VMP and VMP, respectively, for patients ≥75 years of age, and 48.6 mg/m² and 46.2 mg/m² with D-VMP and VMP, respectively, for patients <75 years of age
- By the end of Cycle 9, more VMP patients discontinued treatment compared with D-VMP patients in both age groups (**Table 2**)

Table 1. Demographics and Baseline Characteristics of the ITT Population by Age Group (N = 706)

	≥75 years		<75 years	
Characteristic	D-VMP (n = 104)	VMP (n = 107)	D-VMP (n = 246)	VMP (n = 249)
Age				
Median (range), years	78 (75-93)	77 (75-91)	69 (40-74)	69 (50-74)
Male, %	43	47	47	47
ECOG status,[a] %				
0	31	30	19	27
1	46	46	55	50
2	23	24	27	23
ISS stage,[b] %				
I	14	14	22	21
II	45	48	37	44
III	41	38	40	35
Cytogenetic profile[c]				
N	93	90	221	212
Standard risk, %	80	88	85	84
High risk, %	20	12	15	16

ITT, intent-to-treat; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.
[a]ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
[b]Based on the combination of serum ß2-microglobulin and albumin.
[c]Based on fluorescence in situ hybridization/karyotype testing performed at local sites; t(4;14), t(14;16), and del17p were classified as high-risk.

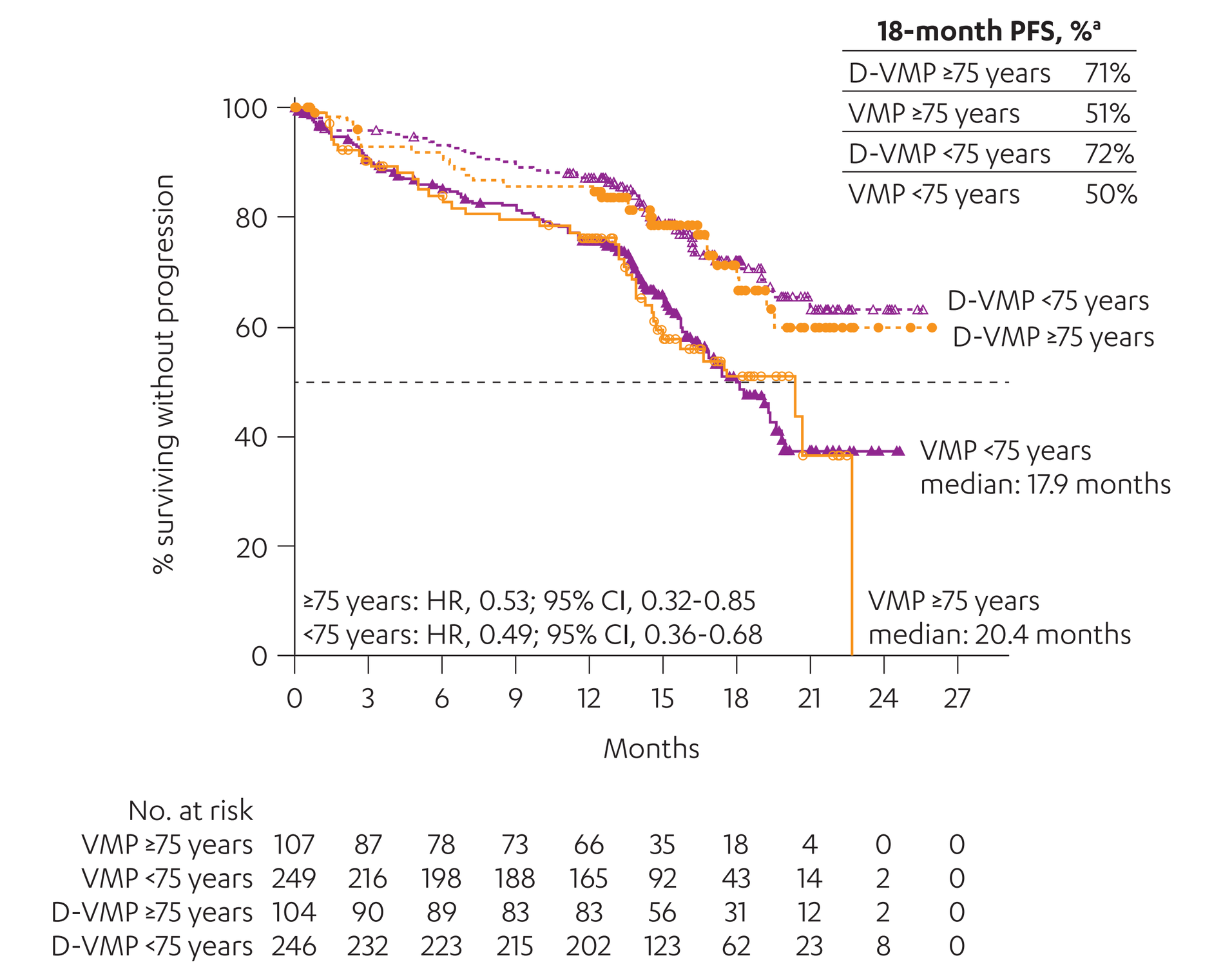
Table 2. Patient Disposition by Age Group

	≥75 years of age			<75 years of age		
	VMP (n = 106)	D-VMP (n = 102)		VMP (n = 248)	D-VMP (n = 244)	
	Cycles 1-9	Cycles 1-9	Cycles 10+	Cycles 1-9	Cycles 1-9	Cycles 10+
Patients who discontinued study treatment, %	43	28	8	29	16	10
Reason for discontinuation, %						
Progressive disease	12	4	6	14	8	10
Adverse event	16	8	0	7	4	0
Death	2	4	1	2	3	<1
Noncompliance with study drug	9	9	1	2	<1	0
Physician decision	2	0	0	2	0	0
Withdrawal by patient	2	1	0	2	<1	0
Other	0	3	0	<1	<1	0

VMP, bortezomib/melphalan/prednisone; D-VMP, daratumumab/bortezomib/melphalan/prednisone.

Efficacy

- In the ITT population, D-VMP reduced the risk of progression or death by 50% (median PFS: D-VMP, not reached vs VMP, 18.1 months; hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.38-0.65; P <0.001)[9]
- Median PFS was prolonged for D-VMP versus VMP in both age groups
  - ≥75 years: not reached with D-VMP versus 20.4 months with VMP (HR, 0.53; 95% CI, 0.32-0.85; **Figure 2**)
  - <75 years: not reached with D-VMP versus 17.9 months with VMP (HR, 0.49; 95% CI, 0.36-0.68; **Figure 2**)



18-month PFS, %[a]
D-VMP ≥75 years 71%
VMP ≥75 years 51%
D-VMP <75 years 72%
VMP <75 years 50%
% surviving without progression
D-VMP <75 years
D-VMP ≥75 years
VMP <75 years median: 17.9 months
≥75 years: HR, 0.53; 95% CI, 0.32-0.85
<75 years: HR, 0.49; 95% CI, 0.36-0.68
VMP ≥75 years median: 20.4 months
Months
No. at risk
VMP ≥75 years 107 87 78 73 66 35 18 4 0 0
VMP <75 years 249 216 198 188 165 92 43 14 2 0
D-VMP ≥75 years 104 90 89 83 83 56 31 12 2 0
D-VMP <75 years 246 232 223 215 202 123 62 23 8 0

PFS, progression-free survival; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Figure 2. PFS by age group.

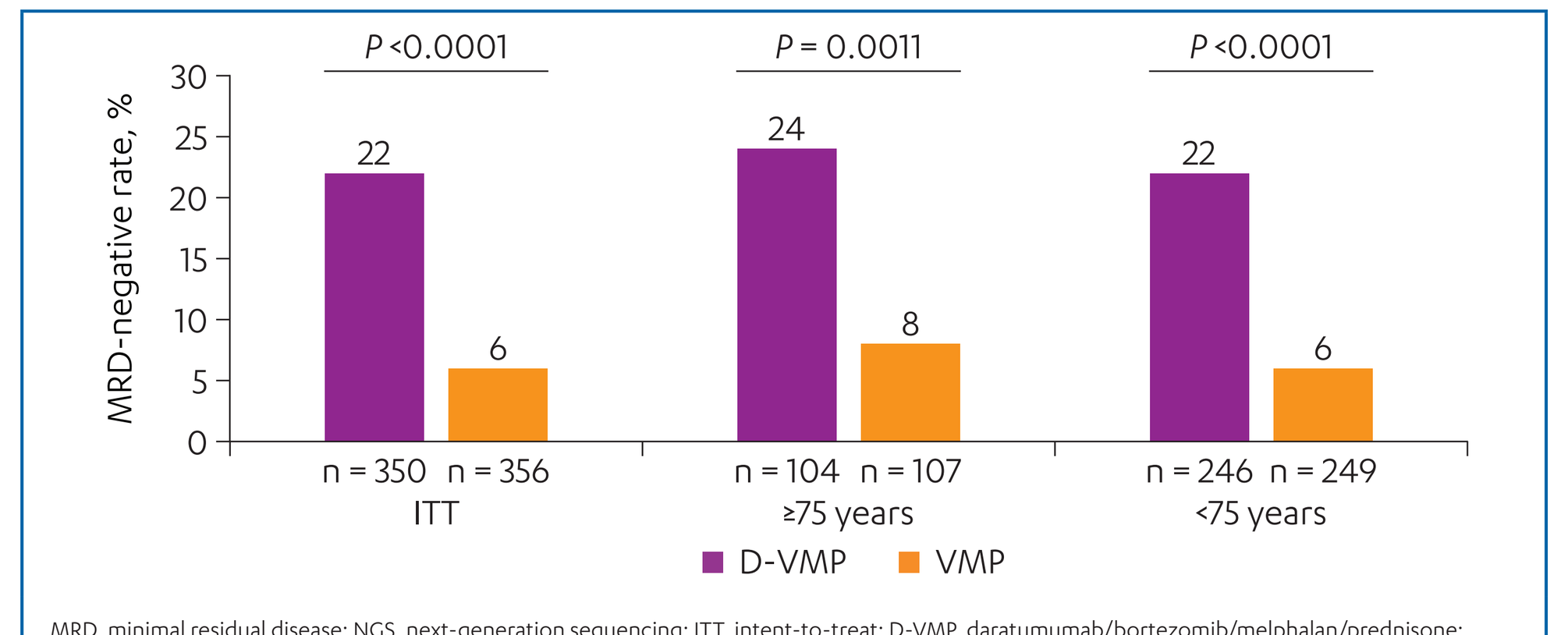
- Patients receiving D-VMP demonstrated higher ORRs and double the rate of stringent CR (sCR) versus those receiving VMP in both age groups (**Table 3**)
- Times to first response were similar across age groups, whereas time to CR was slightly shorter with D-VMP versus VMP for the ≥75-year age group only (**Table 3**)

Table 3. Response Rates and Characteristics by Age Group

	ITT		≥75 years		<75 years	
Response characteristic	D-VMP (n = 350)	VMP (n = 356)	D-VMP (n = 104)	VMP (n = 107)	D-VMP (n = 246)	VMP (n = 249)
ORR, %	90.9	73.9	87.5	70.1	92.3	75.5
sCR, %	18.0	7.0	19.2	6.5	17.5	7.2
≥CR, %	42.6	24.4	41.3	24.3	43.1	24.5
≥VGPR, %	71.1	49.7	68.3	48.6	72.4	50.2
Median (range) time to first response,[a] months	0.79 (0.4-15.5)	0.82 (0.7-12.6)	0.82 (0.7-15.5)	0.82 (0.7-6.3)	0.79 (0.4-15.3)	0.85 (0.7-12.6)
Median (range) time to CR or better,[a] months	8.31 (1.9-21.0)	7.46 (0.7-20.5)	6.93 (2.6-21.0)	9.00 (0.7-14.0)	8.41 (1.9-18.3)	7.10 (1.4-20.5)

ITT, intent-to-treat; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ORR, overall response rate; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MM, multiple myeloma.
[a]Response of PR or better in response-evaluable population (ie, patients who have a confirmed diagnosis of MM and measurable disease at baseline and must have received ≥1 component of study treatment and have adequate post-baseline disease assessments).

- The MRD-negativity rate (10^{-5} sensitivity threshold) was increased with D-VMP versus VMP in patients ≥75 years of age (24% vs 8%; *P* = 0.0011) and <75 years of age (22% vs 6%; *P* <0.0001), consistent with the ITT population[8] (22% vs 6%; *P* <0.0001; **Figure 3**)



MRD, minimal residual disease; NGS, next-generation sequencing; ITT, intent-to-treat; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; CR, complete response.
[a]Assessed at the time of confirmation of CR/stringent CR and, if confirmed, at 12, 18, 24, and 30 months after first dose following protocol amendment 4 (originally 14, 20, and 26 months).

Figure 3. MRD[a] as assessed by NGS at the 10^{-5} sensitivity threshold by age group.

Safety

- The most common (≥25%) all-grade (≥25%) treatment-emergent adverse events (TEAEs) and TEAEs of interest (peripheral sensory neuropathy and infections) are summarized in **Table 4**
- Overall rates of grade 3/4 TEAEs in the overall population were 78% for D-VMP and 77% for VMP
  - Grade 3/4 TEAEs were reported in 89% and 85% of patients aged ≥75 years receiving D-VMP and VMP, respectively, and in 73% and 74% of patients aged <75 years receiving D-VMP and VMP, respectively
- The most common (≥10%) grade 3/4 TEAEs and TEAEs of interest (peripheral sensory neuropathy and infections) are summarized in **Table 5**
- In the D-VMP arm, infusion-related reactions were observed in 36% (9% grade 3/4) of patients aged ≥75 years and 24% (3% grade 3/4) of patients aged <75 years; most occurred during the first infusion
- Among patients aged ≥75 years, second primary malignancies (SPMs) were observed in 6 D-VMP versus 2 VMP patients; in patients aged <75 years, SPMs were observed in 2 D-VMP versus 7 VMP patients

Table 4. Most Common (≥25%) All-grade TEAEs and Incidences of Peripheral Sensory Neuropathy and Infections

	Overall population[a]		≥75 years		<75 years	
All-grade TEAEs	D-VMP (n = 346)	VMP (n = 354)	D-VMP (n = 102)	VMP (n = 106)	D-VMP (n = 244)	VMP (n = 248)
Most common (≥25%) TEAEs, %						
Neutropenia	50	53	62	55	45	52
Thrombocytopenia	49	54	65	59	42	51
Anemia	28	38	36	42	25	36
URTI	26	14	28	15	26	13
Diarrhea	24	25	30	33	21	21
Pyrexia	23	21	31	20	20	21
Nausea	21	22	26	30	19	18
Peripheral sensory neuropathy, %	28	34	24	40	30	32
Infections,[b] %	67	48	73	52	64	46

TEAE, treatment-emergent adverse event; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; URTI, upper respiratory tract infection; MedDRA, *Medical Dictionary for Regulatory Activities*.
[a]Includes all patients who received ≥1 dose of study treatment.
[b]MedDRA system organ class.

Table 5. Most Common (≥10%) Grade 3/4 TEAEs and Incidences of Peripheral Sensory Neuropathy and Infections

	Overall population[a]		≥75 years		<75 years	
Grade 3/4 TEAEs	D-VMP (n = 346)	VMP (n = 354)	D-VMP (n = 102)	VMP (n = 106)	D-VMP (n = 244)	VMP (n = 248)
Patients with grade 3/4 TEAEs, %	78	77	89	85	73	74
Most common (≥10%) TEAEs, %						
Neutropenia	40	39	52	42	35	38
Thrombocytopenia	34	38	51	43	28	35
Anemia	16	20	24	23	13	19
Leukopenia	8	9	13	9	6	9
Lymphopenia	8	6	10	10	7	4
Pneumonia	11	4	18	9	9	2
Peripheral sensory neuropathy, %	1	4	0	6	2	3
Infections,[b] %	23	15	28	20	21	13

TEAE, treatment-emergent adverse event; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; MedDRA, *Medical Dictionary for Regulatory Activities*.
[a]Includes all patients who received ≥1 dose of study treatment.
[b]MedDRA system organ class.

CONCLUSIONS

- **Efficacy of D-VMP in patients ≥75 years of age was consistent with the ITT population**
  - **D-VMP reduced the risk of progression or death by 47% and 51% in patients aged ≥75 years and <75 years, respectively**
  - **D-VMP induced deeper responses (2-fold increase in sCR rates) and higher rates of MRD negativity (≥3-fold higher) at a 10^{-5} sensitivity threshold**
  - **First randomized phase 3 study to demonstrate MRD negativity using NGS in NDMM patients ≥75 years of age**
- **D-VMP had acceptable tolerability regardless of age**
  - **No new safety signals were observed**
  - **Grade 3/4 infection rates were consistent with the overall population**
  - **Grade 3/4 peripheral sensory neuropathy remained low with D-VMP across age groups**
- **D-VMP was efficacious and well tolerated in patients aged ≥75 years with NDMM**

REFERENCES

1. Moreau P, et al. *Ann Oncol*. 2017;28(suppl 4):iv52-iv61.
2. San Miguel JF, et al. *N Engl J Med*. 2008;359(9):906-917.
3. Harousseau JL, et al. *Blood*. 2010;116(19):3743-3750.
4. Mateos MV, et al. *Lancet Oncol*. 2010;11(10):934-941.
5. Palumbo A, et al. *J Clin Oncol*. 2010;28(34):5101-5109.
6. Touzeau C, Moreau P. *Expert Opin Biol Ther*. 2017;17(7):887-893.
7. Blair HA. *Drugs*. 2017;77(18):2013-2024.
8. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc; 2018.
9. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528.

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DISCLOSURES

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