Disclosures

- **Consultation:** Bristol-Myers Squibb, Celgene, Amgen, Janssen, Takeda
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- **Travel expenses:** Janssen, Celgene

Daratumumab Plus Bortezomib-Melphalan-Prednisone (VMP) in Elderly (≥75 Years of Age) Patients With Newly Diagnosed Multiple Myeloma Ineligible for Transplantation (ALCYONE)

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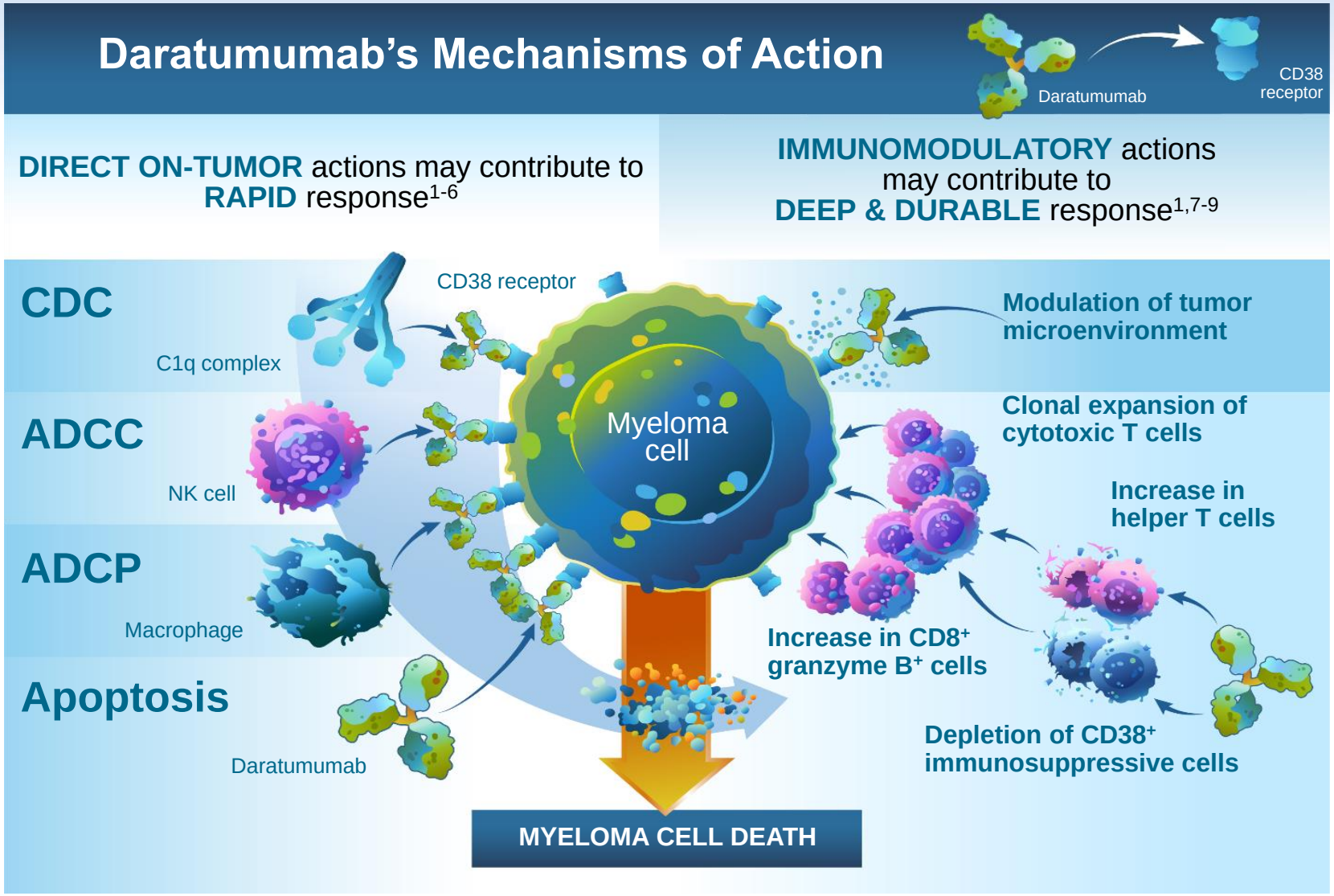
Background: Elderly MM Population

- The median age at diagnosis of MM is approximately 70 years, and 35 to 40% of patients are >75 years of age[1]
- Elderly patients often have low performance status, increased comorbidities, and reduced organ function, affecting their ability to tolerate MM treatment or participate in clinical trials[2]
  - In practice, patients with NDMM who are ≥70 years of age or have significant comorbidities are usually ineligible for ASCT[3]
  - VMP is a standard of care for elderly patients who are not eligible for ASCT
- Subgroup analyses of clinical trial data are needed for elderly patients with MM, especially those >75 years of age

MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem cell transplantation; VMP, bortezomib/melphalan/prednisone.

1. Zweegman S, et al. *Haematologica*. 2014;99(7):1133-1137.
2. Madan S, Kumar S. *Therapy*. 2011;8(4):415-429.
3. Moreau P, et al. *Ann Oncol*. 2017;28(suppl 4):iv52-iv61.

Background: Daratumumab

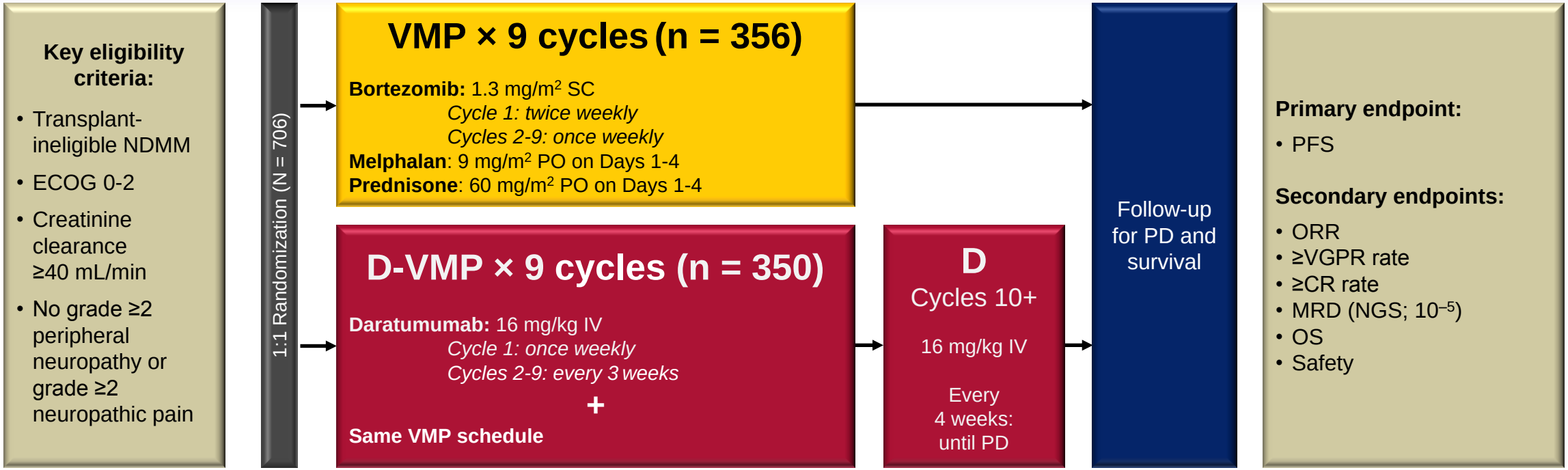


- Daratumumab
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action
- Approved
  - As monotherapy and in combination with standard of care regimens in RRMM in many countries
  - In combination with bortezomib, melphalan, and prednisone in non-transplant NDMM (United States, Brazil, etc.)
- Efficacy
  - Daratumumab-based combinations reduce risk of progression or death and induce rapid, deep, and durable responses in RRMM and NDMM[10-12]

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; RRMM, relapsed/refractory multiple myeloma.

1. DARZALEX US PI; 2018. 2. Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. 3. Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. 4. Overdijk MB, et al. *mABs*. 2015;7(2):311-321. 5. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. *Blood*. 2012;120:73. 7. Krejcik J, et al. *Blood*. 2016;128(3):384-394. 8. Adams H, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. 9. Chiu C, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. 10. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 11. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 12. Mateos MV, et al. *N Engl J Med*. 2018;378:518-528.

ALCYONE: Study Design



Stratification factors
- ISS (I vs II vs III)
- Region (Europe vs other)
- Age (<75 vs ≥75 years)

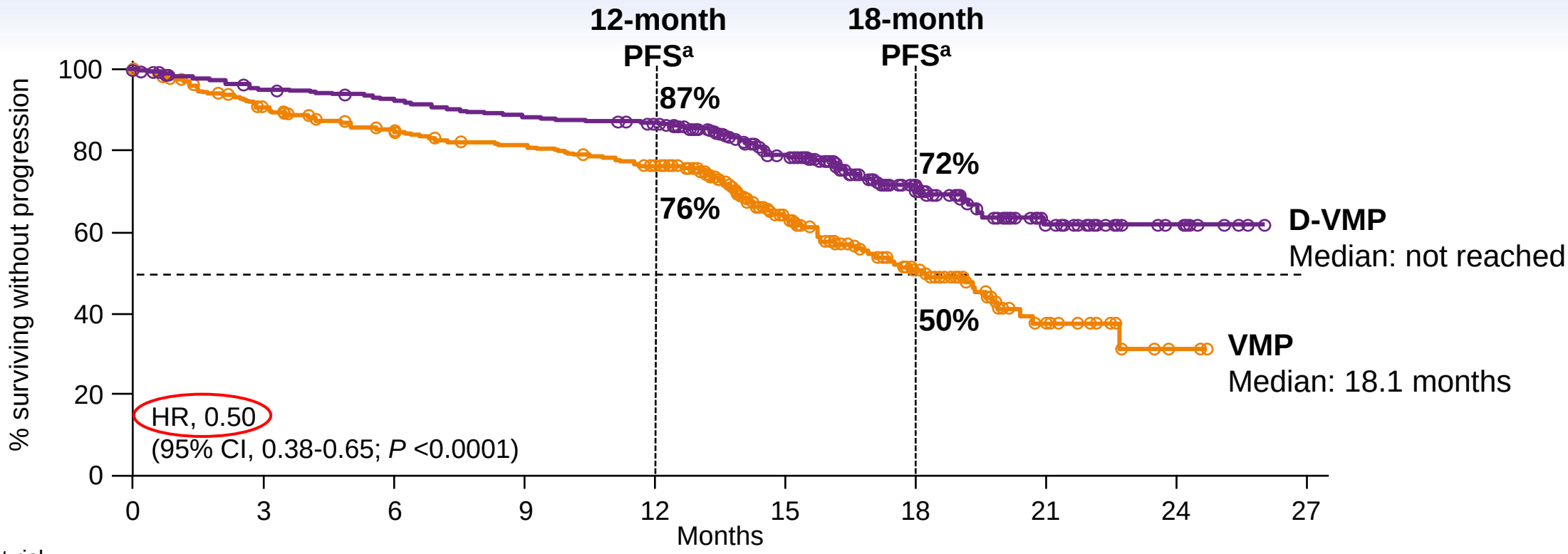
- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

Statistical analyses
- 360 PFS events: 85% power for 8-month PFS improvement[a]
- Interim analysis: ~216 PFS events

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; 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.
[a]8-month PFS improvement over 21-month median PFS of VMP.

Progression-free Survival in the ITT Population

- Median duration of follow-up: 16.5 months (range: 0.1-28.1)



Median PFS not reached for D-VMP versus 18.1 months for VMP;
50% reduction in the risk of progression or death for D-VMP versus VMP

ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.
Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528.

Demographics and Baseline Characteristics

	≥75 years		<75 years	
	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

[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 β2-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.

Patient Disposition

	≥75 years			<75 years		
	VMP[a] (n = 106)	D-VMP[a] (n = 102)		VMP[a] (n = 248)	D-VMP[a] (n = 244)	
	Cycles 1-9	Cycles 1-9	Cycles 10+	Cycles 1-9	Cycles 1-9	Cycles 10+
Patients who discontinued study treatment, n (%)	45 (43)	29 (28)	8 (8)	72 (29)	38 (16)	25 (10)
Reason for discontinuation, n (%)						
Progressive disease	13 (12)	4 (4)	6 (6)	34 (14)	19 (8)	24 (10)
Adverse event	17 (16)	8 (8)	0	16 (7)	9 (4)	0
Death	2 (2)	4 (4)	1 (1)	6 (2)	7 (3)	1 (<1)
Noncompliance with study drug	9 (9)	9 (9)	1 (1)	6 (2)	1 (<1)	0
Physician decision	2 (2)	0	0	5 (2)	0	0
Withdrawal by patient	2 (2)	1 (1)	0	4 (2)	1 (<1)	0
Other	0	3 (3)	0	1 (<1)	1 (<1)	0

By end of Cycle 9, more VMP-treated patients discontinued treatment compared with D-VMP-treated patients in both age groups

[a]VMP was administered only during the first 9 cycles.

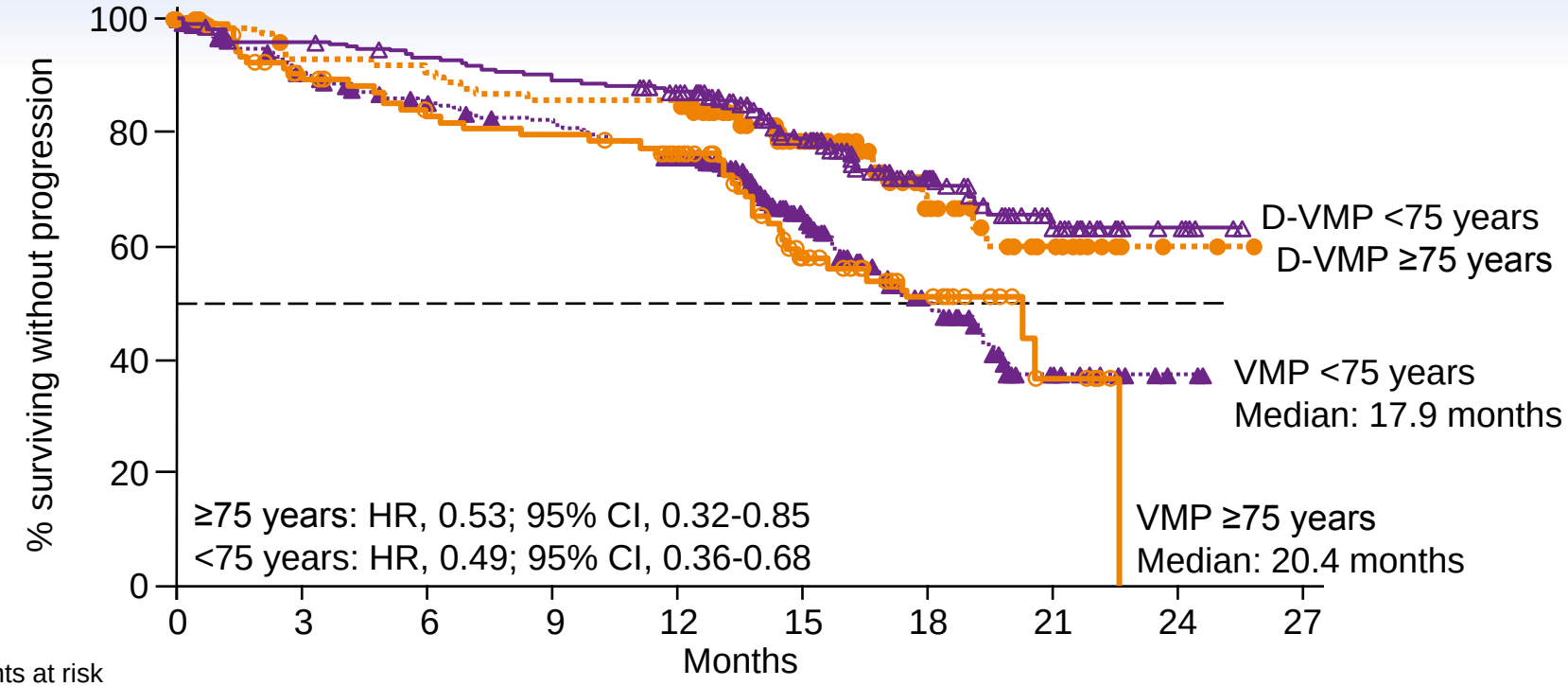
Bortezomib Exposure

	≥75 years		<75 years	
	D-VMP (n = 102)	VMP (n = 106)	D-VMP (n = 244)	VMP (n = 248)
Patients who completed 9 planned cycles of treatment, n (%)	74 (73)	55 (52)	202 (83)	165 (67)
Median (range) cumulative dose of bortezomib received, mg/m²	43.1 (1.3-53.2)	34.1 (3.9-53.6)	48.6 (1.3-55.3)	46.2 (2.6-55.0)
Median (range) relative bortezomib dose intensity, %	88.3 (12.1-102.3)	85.6 (36.5-110.6)	96.9 (26.8-106.3)	95.7 (26.2-105.8)

Median cumulative bortezomib exposure reflects proportion of patients completing 9 VMP cycles

Efficacy: Progression-free Survival

- Median duration of follow-up: 16.5 months (range: 0.1-28.1)



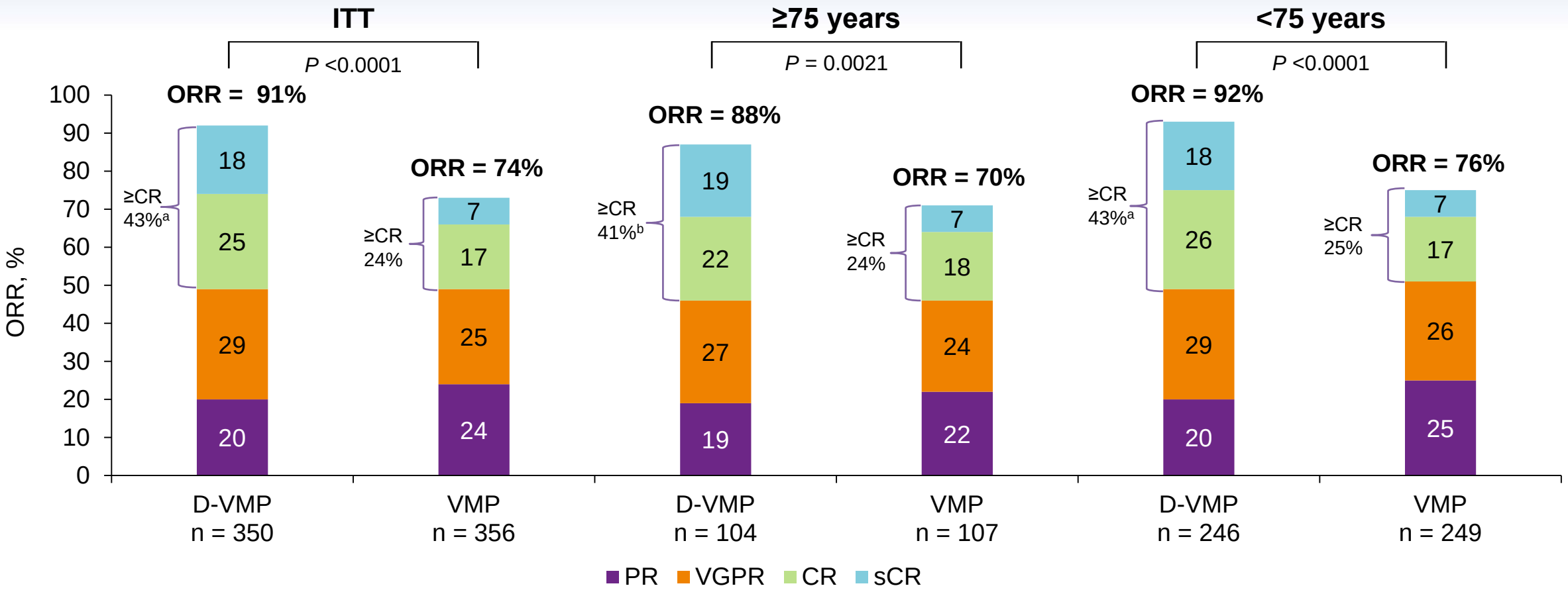
Patients at risk										
VMP ≥75 years	107	87	78	73	66	35	18	4	0	0
VMP <75 years	249	216	198	188	165	92	43	14	2	0
D-VMP ≥75 years	104	90	89	83	83	56	31	12	2	0
D-VMP <75 years	246	232	223	215	202	123	62	23	8	0

18-month PFS, %[a]	D-VMP	VMP
≥75 years	71	51
<75 years	72	50

D-VMP reduced the risk of progression or death by 47% in the ≥75 years age group and 51% in the <75 years age group

[a]Kaplan-Meier estimate.

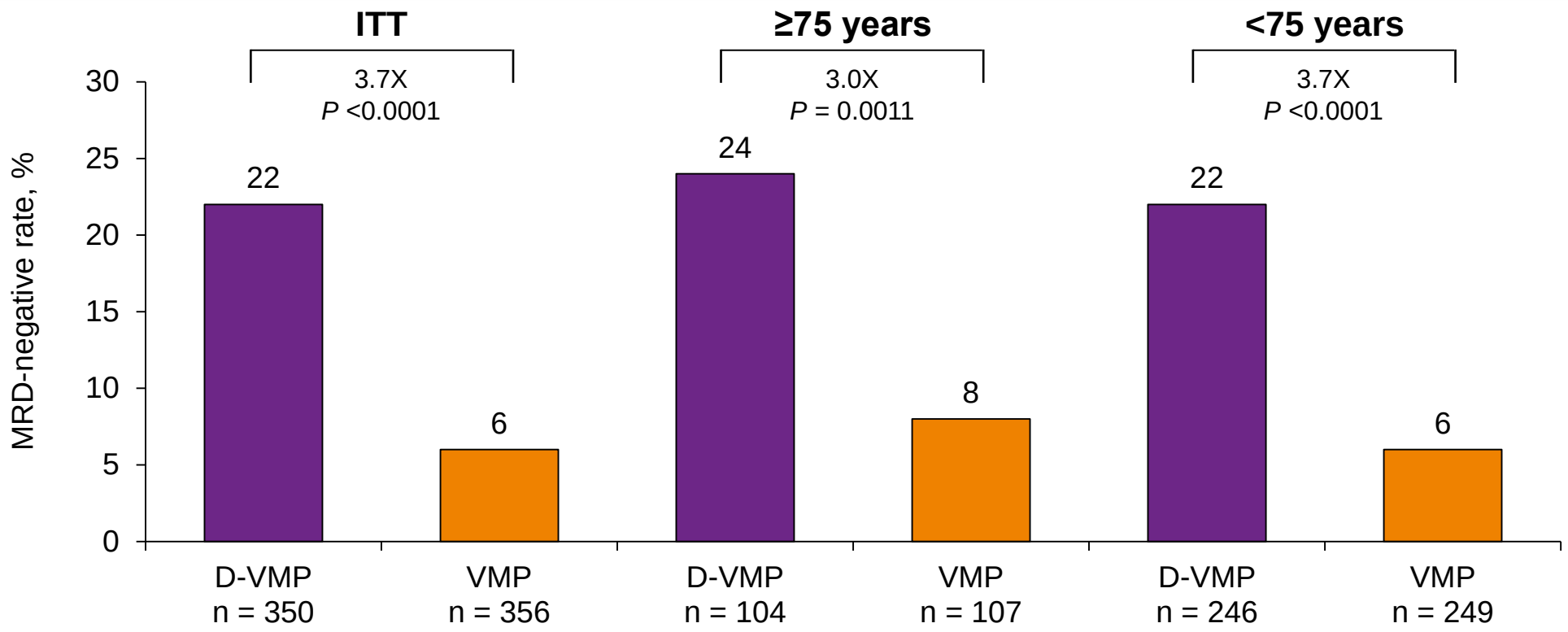
Efficacy: Overall Response Rate



D-VMP induced deeper responses (≥2-fold higher rates of sCR) regardless of age

PR, partial response; sCR, stringent complete response.
[a]*P* <0.0001 for D-VMP vs VMP.
[b]*P* = 0.0085 for D-VMP vs VMP.

Efficacy: MRD-negative Rates (10^{-5})[a]



D-VMP induced ≥3-fold higher rates of MRD negativity regardless of age

[a]Assessed at time of confirmation of CR/sCR and, if confirmed, at 12, 18, 24, and 30 months after first dose following protocol amendment 4 (originally 14, 20, and 26 months).

Most Common (≥25%) TEAEs

All-grade TEAEs	Overall population[a]		≥75 years[a]		<75 years[a]	
	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; URTI, upper respiratory tract infection; MedDRA, Medical Dictionary for Regulatory Activities.
[a]Safety population, which includes all patients who received ≥1 dose of study treatment.
[b]MedDRA system organ class.

Most Common (≥10%) Grade 3/4 TEAEs

	Overall population[a]		≥75 years[a]		<75 years[a]	
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 TEAE, %	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
Pneumonia	11	4	18	9	9	2
Leukopenia	8	9	13	9	6	9
Lymphopenia	8	6	10	10	7	4
Peripheral sensory neuropathy, %	1	4	0	6	2	3
Infections,[b] %	23	15	28	20	21	13

Peripheral sensory neuropathy and infection rates were consistent with overall population

[a]Safety population, which includes all patients who received ≥1 dose of study treatment.
[b]MedDRA system organ class.

Additional Safety Findings

	≥75 years		<75 years	
	D-VMP (n = 102)	VMP (n = 106)	D-VMP (n = 244)	VMP (n = 248)
Patients who discontinued treatment due to TEAEs, %	8	16	4	6
Patients with IRRs, %	36	-	24	-
Grade 3/4	9	-	3	-
Patients with SPMs, %	6	2	<1	3

- Most IRRs occurred during the first infusion

- **Low rates of discontinuation due to TEAEs with D-VMP in both age groups**
- **SPM rate for ≥75 years subgroup is consistent with other daratumumab studies**

IRR, infusion-related reaction; SPM, second primary malignancy.

Conclusions

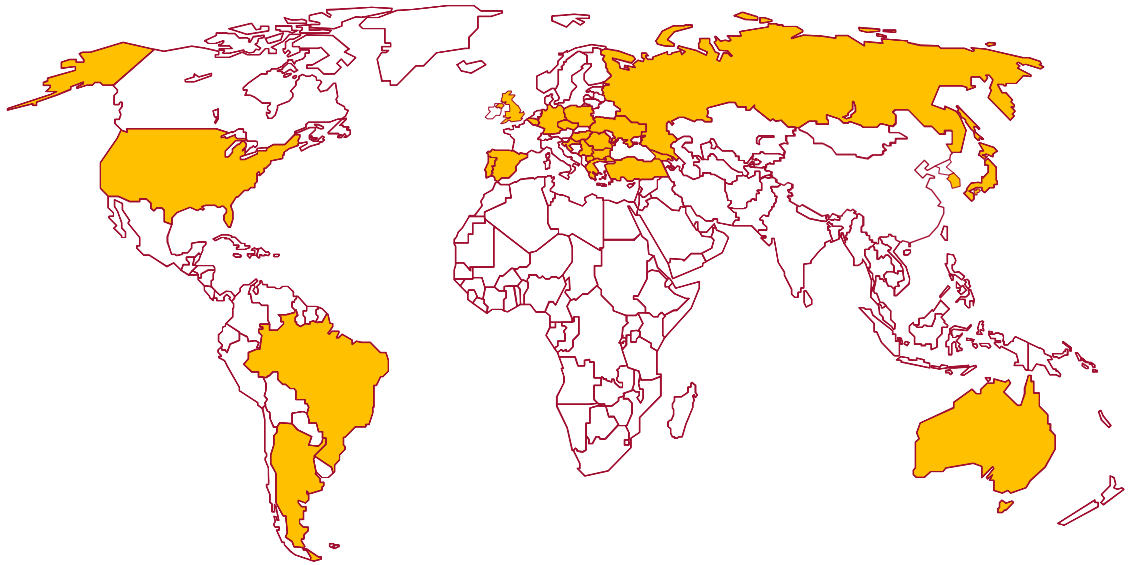
- Efficacy of D-VMP in patients aged ≥75 years of age was consistent with the ITT population
  - D-VMP reduced the risk of progression or death by 47% and 51% in patients aged ≥75 years and <75 years, respectively
  - D-VMP induced deeper responses (2-fold increase in sCR rates) and higher rates of MRD negativity (≥3-fold higher) at a 10^{-5} sensitivity threshold
- First randomized phase 3 study to demonstrate MRD negativity 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 those observed in the overall population
  - Grade 3/4 peripheral sensory neuropathy remained low with D-VMP across age groups

Combining daratumumab with VMP provides significant clinical benefit, regardless of age

Acknowledgments

- Patients who participated in these studies
- Staff members at the study sites
- Data and safety monitoring committee
- Staff members involved in data collection and analyses

ALCYONE
25 countries



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