Daratumumab + Bortezomib/Lenalidomide/Dexamethasone in Transplant-eligible Patients With Newly Diagnosed Multiple Myeloma: Analysis of Minimal Residual Disease in the PERSEUS Trial*

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https://www.congresshub.com/Oncology/EHA2024/Daratumumab/Sonneveld

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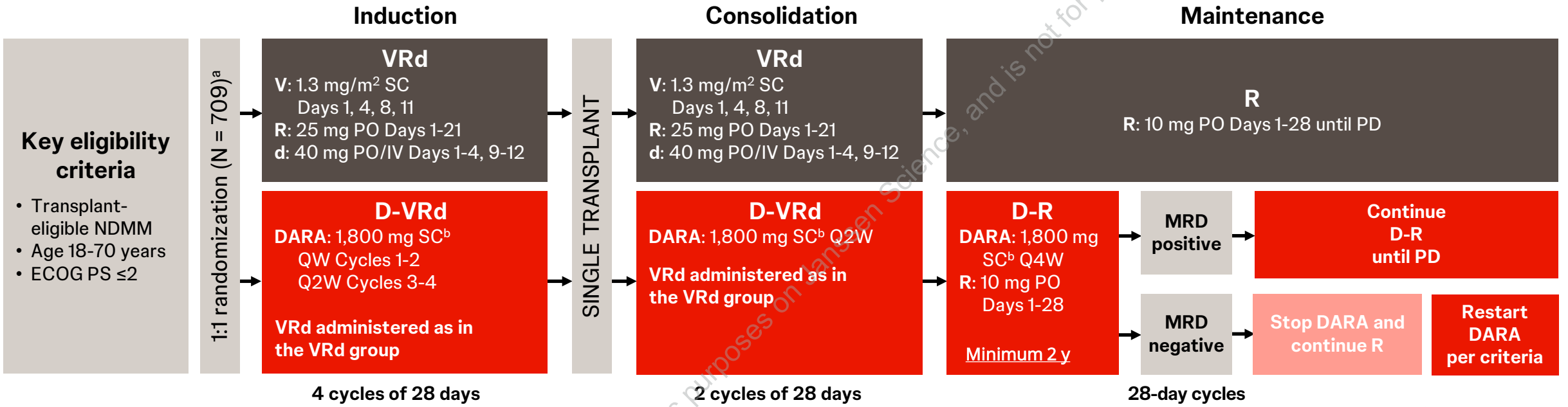
PERSEUS: Introduction

- In NDMM, MRD negativity has been associated with longer PFS and OS, and deeper responses (10^{-6}) have been associated with superior PFS compared with MRD negativity at 10^{-5} or 10^{-4} sensitivity[1,2]
- An increasing number of patients are achieving OS of 10 years or longer. Current MRD testing at a sensitivity level of 10^{-6} and sustained MRD at this level for over 5 years translates into very long survival and potentially a "cure" for patients with standard-risk features[3-5]
- In the primary analysis of PERSEUS, D-VRd induction/consolidation + D-R maintenance improved depth of response and PFS versus VRd induction/consolidation + R maintenance in transplant-eligible NDMM[6]
  - 64% of patients receiving D-R maintenance stopped DARA after ≥2 years due to achieving sustained MRD negativity (10^{-5})[a]
- **Here, we report further results from PERSEUS on deepening of response and MRD negativity during maintenance therapy**

NDMM, newly diagnosed multiple myeloma; MRD, minimal residual disease; PFS, progression-free survival; OS, overall survival; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; D-R, daratumumab plus lenalidomide; VRd, bortezomib/lenalidomide/dexamethasone; R, lenalidomide; DARA, daratumumab; CR, complete response; ITT, intent-to-treat; NGS, next-generation sequencing.
[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA).

1. Munshi NC, et al. *Blood Adv*. 2020;4(23):5988-5999. 2. Perrot A, et al. *Blood*. 2018;132(23):2456-2464. 3. International Myeloma Foundation. A deeper understanding of 'cure' in multiple myeloma. https://www.myeloma.org/blog/dr-duries/deeper-understanding-of-cure-in-myeloma. Accessed May 14, 2024. 4. Engelhardt M, et al. *Haematologica*. 2024. doi:10.3324/haematol.2023.283058. 5. Rodriguez-Otero P, et al. *Cancer Treat Rev*. 2021;100:102284. 6. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313.

PERSEUS: Study Design



Primary endpoint: PFS[c]

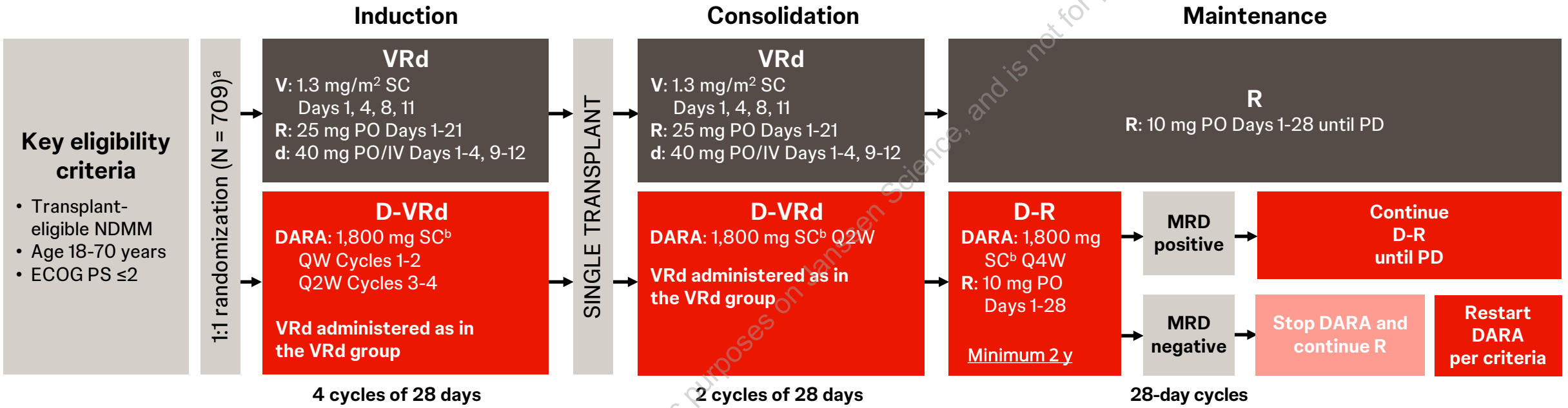
Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate (10^{-5}),[d] OS

Stop DARA therapy after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity (10^{-5})

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate (10^{-5}),[d] OS

Stop DARA therapy after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity (10^{-5})

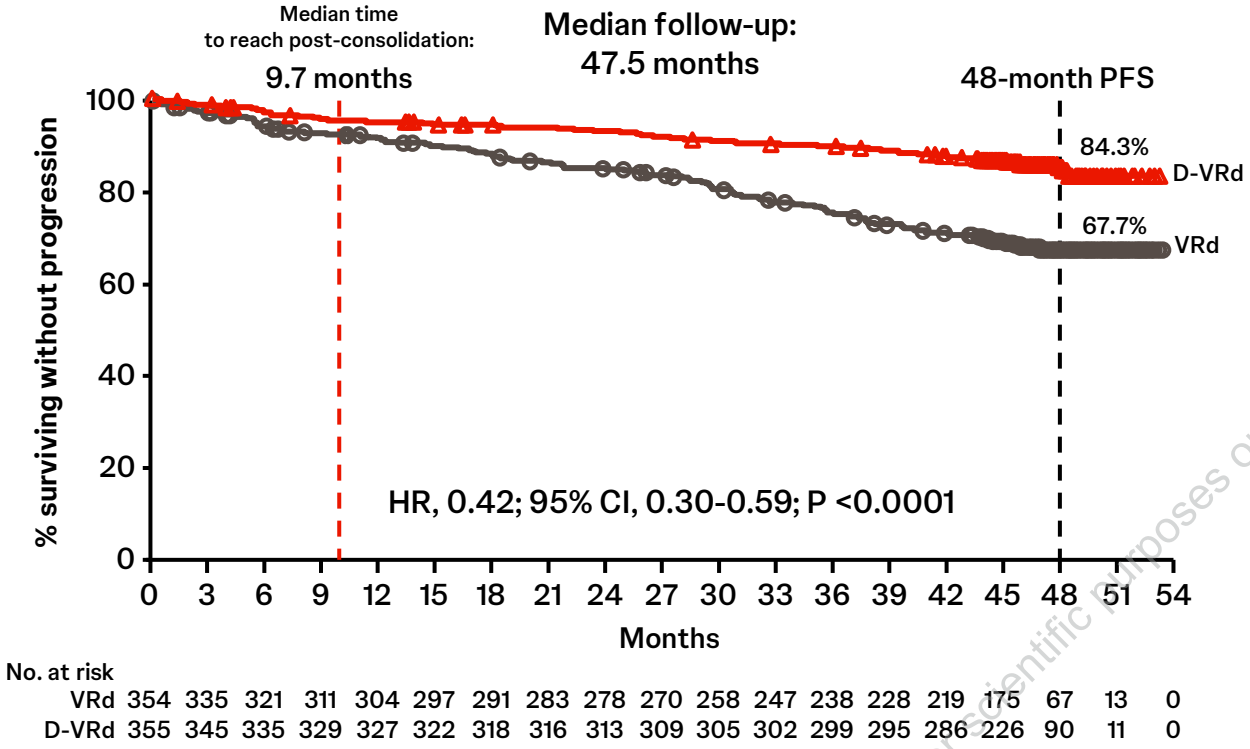
Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

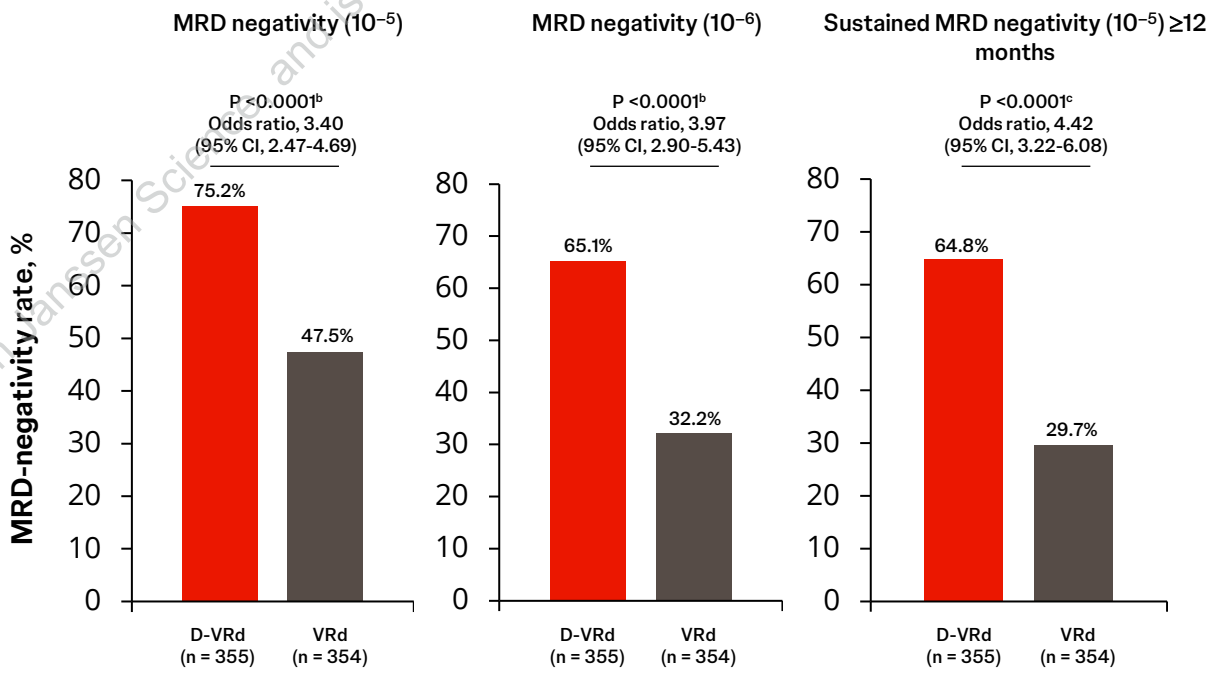
MRD response-adapted approach in maintenance:

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive.

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

PERSEUS Primary Analysis: D-VRd Followed by D-R Maintenance Significantly Improved PFS and Depth of Response Versus VRd Followed by R Maintenance[1]





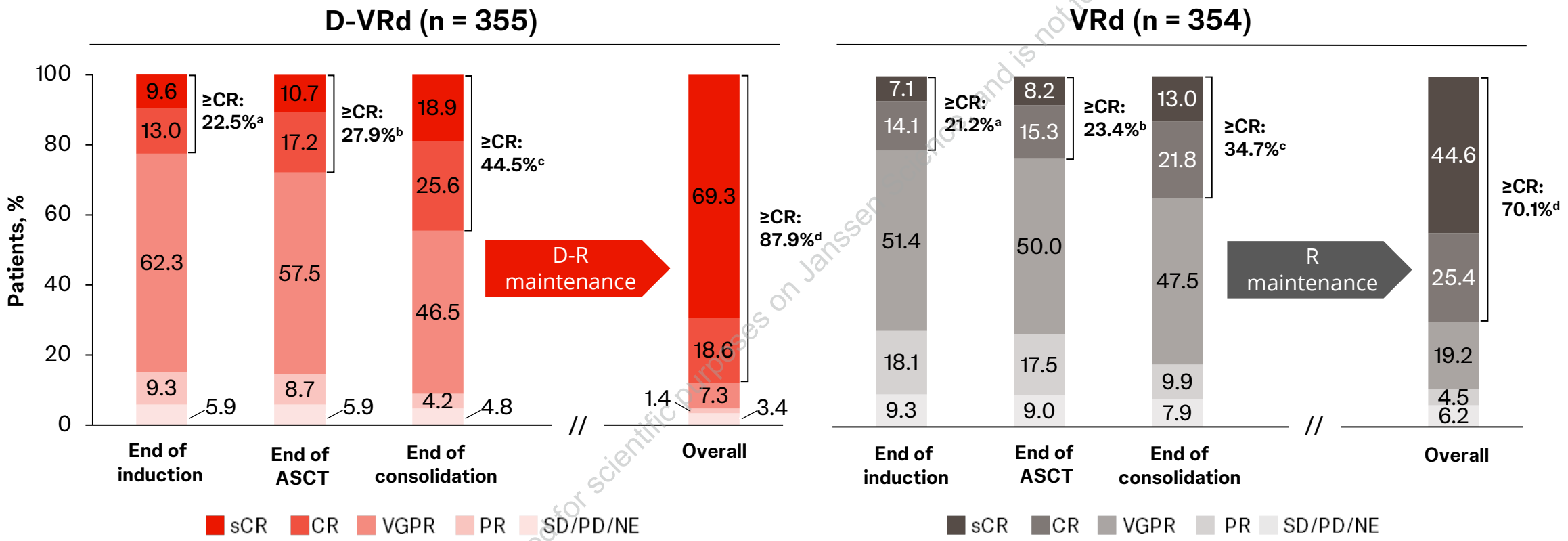
58% reduction in the risk of progression or death in patients receiving D-VRd

Deep and durable MRD negativity achieved with D-VRd

HR, hazard ratio; CI, confidence interval. [a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). [b]*P* values were calculated with the use of the stratified Cochran–Mantel–Haenszel chi-square test. [c]*P* value was calculated with the use of Fisher's exact test.

1. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313.

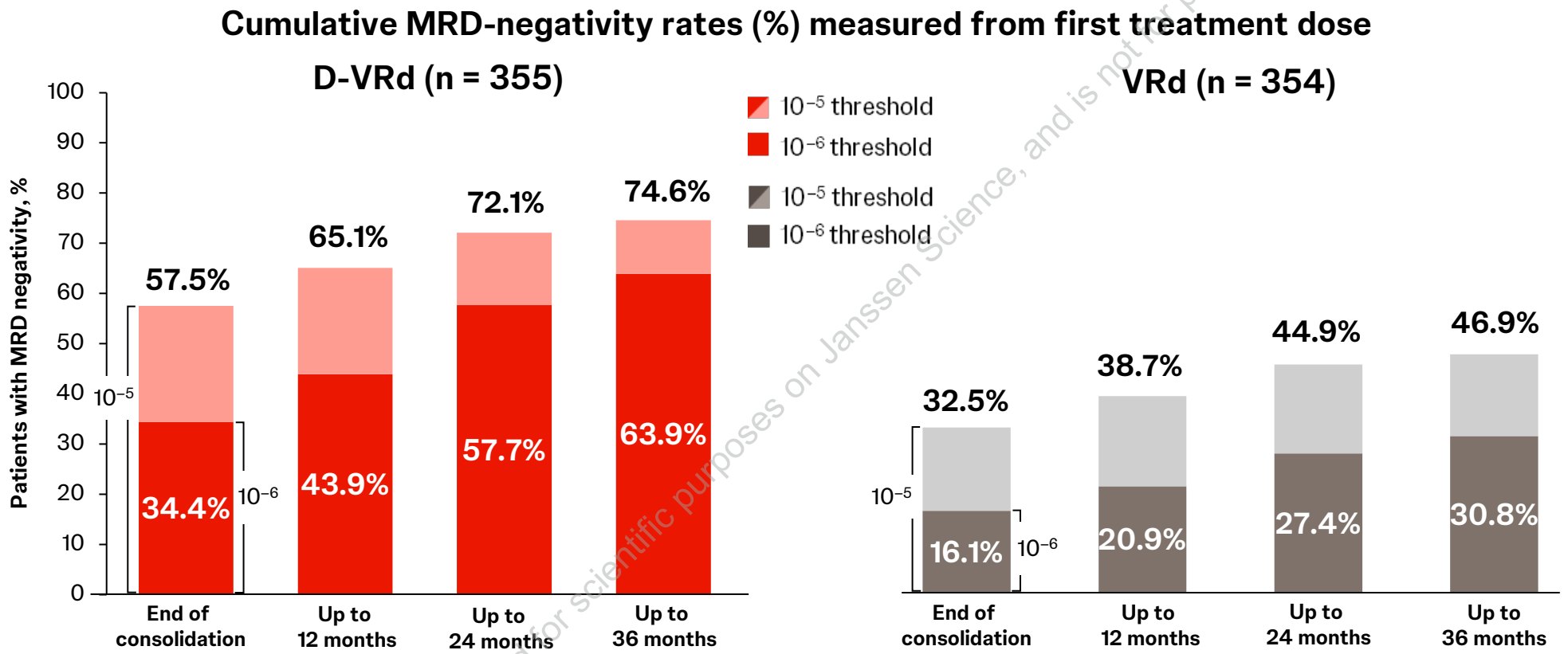
PERSEUS: Responses Over Time (ITT)



Responses deepened to a greater extent with D-VRd + D-R versus VRd + R

ASCT, autologous stem cell transplant; sCR, stringent complete response; PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable. *P* values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test. [a]*P* = 0.6680. [b]*P* = 0.1774. [c]*P* = 0.0078. [d]*P* <0.0001.

PERSEUS: MRD-negativity Rates (10^{-5} and 10^{-6}; ITT)



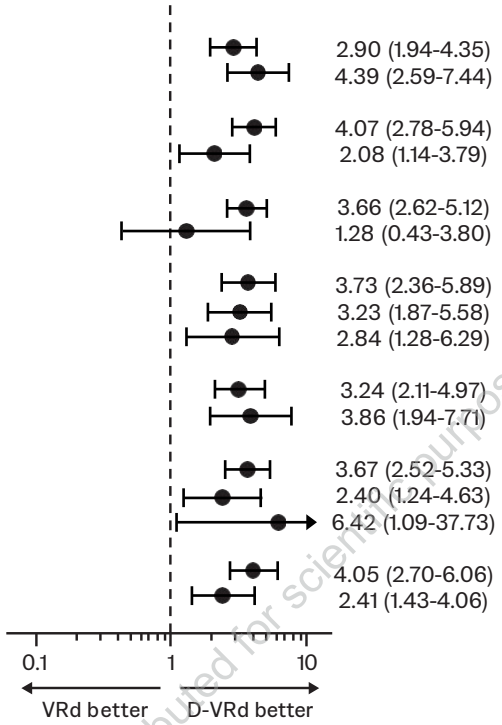
- **D-VRd + D-R doubled the rates of deeper MRD negativity at 10^{-6} versus VRd + R**
- **MRD negativity at 10^{-6} increased by approximately 30% during maintenance with D-R**

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. *P* values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test. *P* <0.0001 for all comparisons of D-VRd versus VRd.

PERSEUS: MRD-negativity Rates in Prespecified Subgroups (ITT)

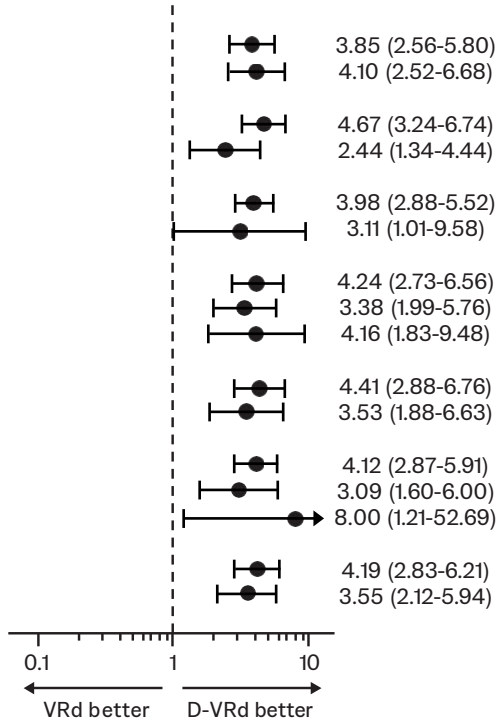
Overall MRD negativity (10^{-5})

Subgroup	VRd n/N (%)	D-VRd n/N (%)	Odds ratio (95% CI)
Sex			
Male	94/205 (45.9)	150/211 (71.1)	2.90 (1.94-4.35)
Female	74/149 (49.7)	117/144 (81.3)	4.39 (2.59-7.44)
Age			
<65 years	125/267 (46.8)	204/261 (78.2)	4.07 (2.78-5.94)
≥65 years	43/87 (49.4)	63/94 (67.0)	2.08 (1.14-3.79)
Race			
White	150/323 (46.4)	251/330 (76.1)	3.66 (2.62-5.12)
Other	18/31 (58.1)	16/25 (64.0)	1.28 (0.43-3.80)
ISS stage			
I	88/178 (49.4)	146/186 (78.5)	3.73 (2.36-5.89)
II	58/125 (46.4)	84/114 (73.7)	3.23 (1.87-5.58)
III	21/50 (42.0)	37/55 (67.3)	2.84 (1.28-6.29)
Type of MM			
IgG	89/185 (48.1)	153/204 (75.0)	3.24 (2.11-4.97)
Non-IgG	50/96 (52.1)	63/78 (80.8)	3.86 (1.94-7.71)
Cytogenetic risk			
Standard risk	128/266 (48.1)	204/264 (77.3)	3.67 (2.52-5.33)
High risk	37/78 (47.4)	52/76 (68.4)	2.40 (1.24-4.63)
Indeterminate	3/10 (30.0)	11/15 (73.3)	6.42 (1.09-37.73)
ECOG PS score			
0	101/230 (43.9)	168/221 (76.0)	4.05 (2.70-6.06)
≥1	67/124 (54.0)	99/134 (73.9)	2.41 (1.43-4.06)



Overall MRD negativity (10^{-6})

Subgroup	VRd n/N (%)	D-VRd n/N (%)	Odds ratio (95% CI)
Sex			
Male	62/205 (30.2)	132/211 (62.6)	3.85 (2.56-5.80)
Female	52/149 (34.9)	99/144 (68.8)	4.10 (2.52-6.68)
Age			
<65 years	83/267 (31.1)	177/261 (67.8)	4.67 (3.24-6.74)
≥65 years	31/87 (35.6)	54/94 (57.4)	2.44 (1.34-4.44)
Race			
White	106/323 (32.8)	218/330 (66.1)	3.98 (2.88-5.52)
Other	8/31 (25.8)	13/25 (52.0)	3.11 (1.01-9.58)
ISS stage			
I	59/178 (33.1)	126/186 (67.7)	4.24 (2.73-6.56)
II	41/125 (32.8)	71/114 (62.3)	3.38 (1.99-5.76)
III	14/50 (28.0)	34/55 (61.8)	4.16 (1.83-9.48)
Type of MM			
IgG	56/185 (30.3)	134/204 (65.7)	4.41 (2.88-6.76)
Non-IgG	36/96 (37.5)	53/78 (67.9)	3.53 (1.88-6.63)
Cytogenetic risk			
Standard risk	88/266 (33.1)	177/264 (67.0)	4.12 (2.87-5.91)
High risk	24/78 (30.8)	44/76 (57.9)	3.09 (1.60-6.00)
Indeterminate	2/10 (20.0)	10/15 (66.7)	8.00 (1.21-52.69)
ECOG PS score			
0	75/230 (32.6)	148/221 (67.0)	4.19 (2.83-6.21)
≥1	39/124 (31.5)	83/134 (61.9)	3.55 (2.12-5.94)



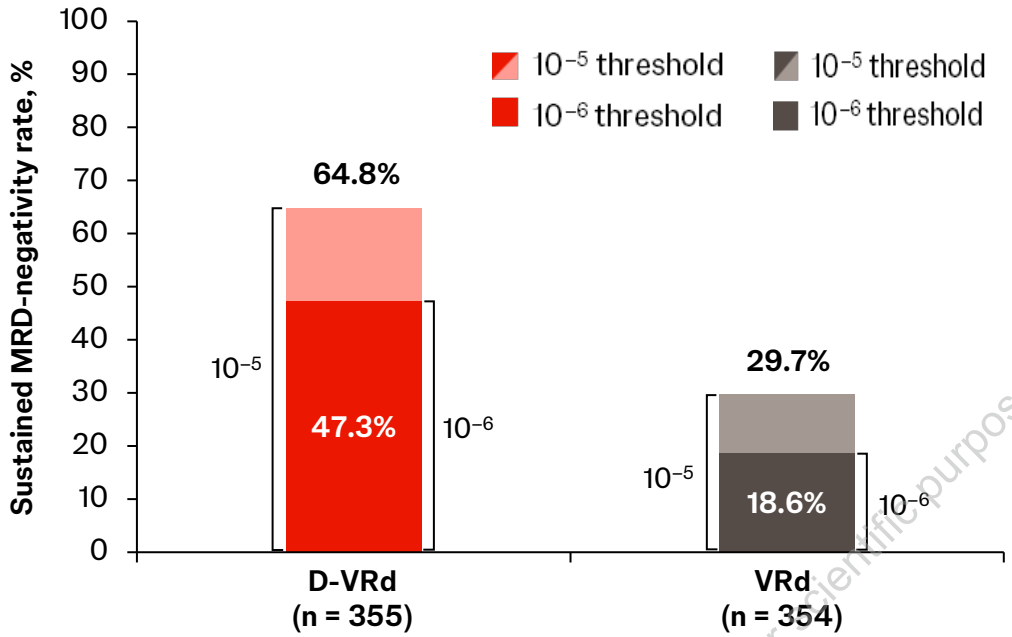
MRD-negativity rates were improved with D-VRd + D-R versus VRd + R across subgroups

MM, multiple myeloma. MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. The subgroup analysis for type of MM was performed on data from patients who had measurable disease in serum. Cytogenetic risk was assessed by fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

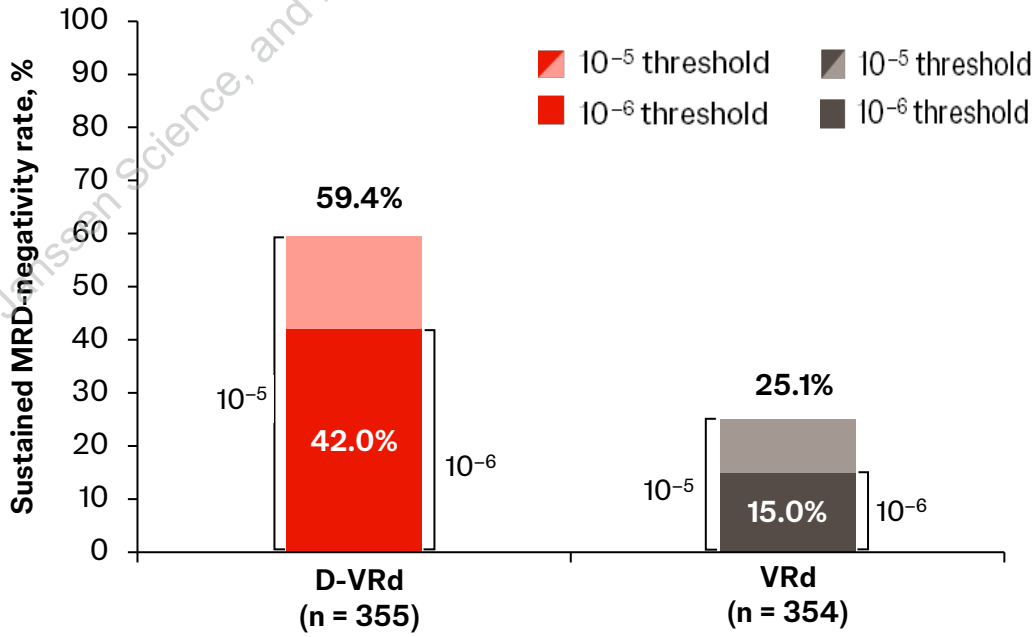
Presented by P Sonneveld at the European Hematology Association (EHA) Hybrid Congress; June 13-16, 2024; Madrid, Spain

PERSEUS: Sustained MRD-negativity Rates (10^{-5} and 10^{-6}; ITT)

Sustained MRD negativity ≥12 months



Sustained MRD negativity ≥18 months



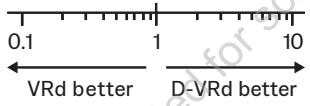
- **Rates of sustained MRD negativity at 10^{-6} were 2.5-fold higher for D-VRd + D-R versus VRd + R**
- **More than 40% of patients had sustained MRD negativity at 10^{-6} for ≥18 months with D-VRd + D-R**

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. *P* values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test. *P* <0.0001 for all comparisons of D-VRd versus VRd.

PERSEUS: Sustained MRD Negativity in Prespecified Subgroups (ITT)

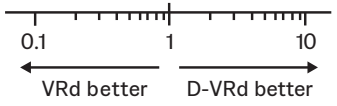
Sustained MRD negativity (10^{-5}) ≥12 months

Subgroup	VRd n/N (%)	D-VRd n/N (%)	Odds ratio (95% CI)
Sex			
Male	62/205 (30.2)	131/211 (62.1)	3.78 (2.51-5.68)
Female	43/149 (28.9)	99/144 (68.8)	5.42 (3.29-8.94)
Age			
<65 years	78/267 (29.2)	180/261 (69.0)	5.38 (3.71-7.81)
≥65 years	27/87 (31.0)	50/94 (53.2)	2.53 (1.37-4.64)
Race			
White	93/323 (28.8)	216/330 (65.5)	4.69 (3.37-6.52)
Other	12/31 (38.7)	14/25 (56.0)	2.02 (0.69-5.88)
ISS stage			
I	58/178 (32.6)	128/186 (68.8)	4.57 (2.94-7.10)
II	35/125 (28.0)	69/114 (60.5)	3.94 (2.29-6.78)
III	12/50 (24.0)	33/55 (60.0)	4.75 (2.04-11.05)
Type of MM			
IgG	50/185 (27.0)	136/204 (66.7)	5.40 (3.49-8.35)
Non-IgG	31/96 (32.3)	52/78 (66.7)	4.19 (2.22-7.92)
Cytogenetic risk			
Standard risk	83/266 (31.2)	183/264 (69.3)	4.98 (3.45-7.20)
High risk	20/78 (25.6)	37/76 (48.7)	2.75 (1.40-5.42)
Indeterminate	2/10 (20.0)	10/15 (66.7)	8.00 (1.21-52.69)
ECOG PS score			
0	71/230 (30.9)	150/221 (67.9)	4.73 (3.18-7.04)
≥1	34/124 (27.4)	80/134 (59.7)	3.92 (2.32-6.62)



Sustained MRD negativity (10^{-6}) ≥12 months

Subgroup	VRd n/N (%)	D-VRd n/N (%)	Odds ratio (95% CI)
Sex			
Male	37/205 (18.0)	96/211 (45.5)	3.79 (2.42-5.93)
Female	29/149 (19.5)	72/144 (50.0)	4.14 (2.46-6.97)
Age			
<65 years	47/267 (17.6)	131/261 (50.2)	4.72 (3.17-7.02)
≥65 years	19/87 (21.8)	37/94 (39.4)	2.32 (1.21-4.48)
Race			
White	63/323 (19.5)	158/330 (47.9)	3.79 (2.67-5.38)
Other	3/31 (9.7)	10/25 (40.0)	6.22 (1.48-26.12)
ISS stage			
I	36/178 (20.2)	93/186 (50.0)	3.94 (2.48-6.28)
II	23/125 (18.4)	47/114 (41.2)	3.11 (1.73-5.59)
III	7/50 (14.0)	28/55 (50.9)	6.37 (2.44-16.60)
Type of MM			
IgG	31/185 (16.8)	96/204 (47.1)	4.42 (2.75-7.09)
Non-IgG	18/96 (18.8)	43/78 (55.1)	5.32 (2.70-10.50
Cytogenetic risk			
Standard risk	54/266 (20.3)	137/264 (51.9)	4.24 (2.88-6.22)
High risk	11/78 (14.1)	23/76 (30.3)	2.64 (1.18-5.90)
Indeterminate	1/10 (10.0)	8/15 (53.3)	10.29 (1.03-102.75)
ECOG PS score			
0	47/230 (20.4)	106/221 (48.0)	3.59 (2.37-5.44)
≥1	19/124 (15.3)	62/134 (46.3)	4.76 (2.62-8.63)

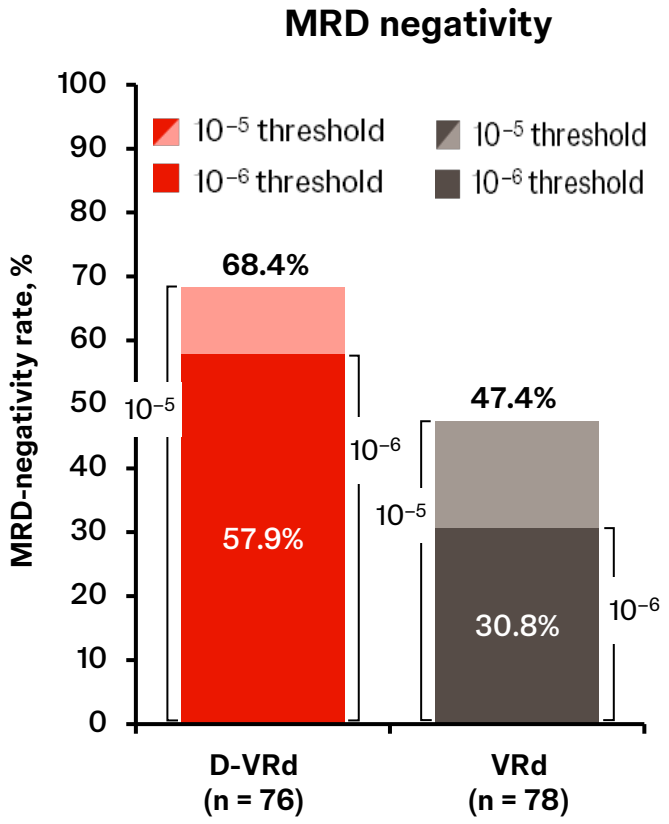


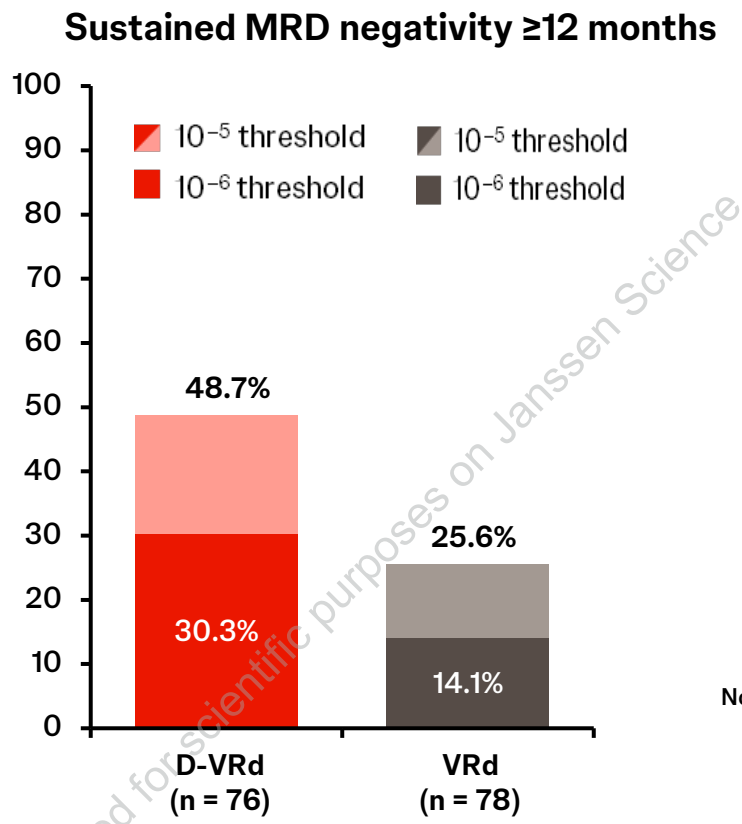
Sustained MRD-negativity rates were improved with D-VRd + D-R versus VRd + R across subgroups

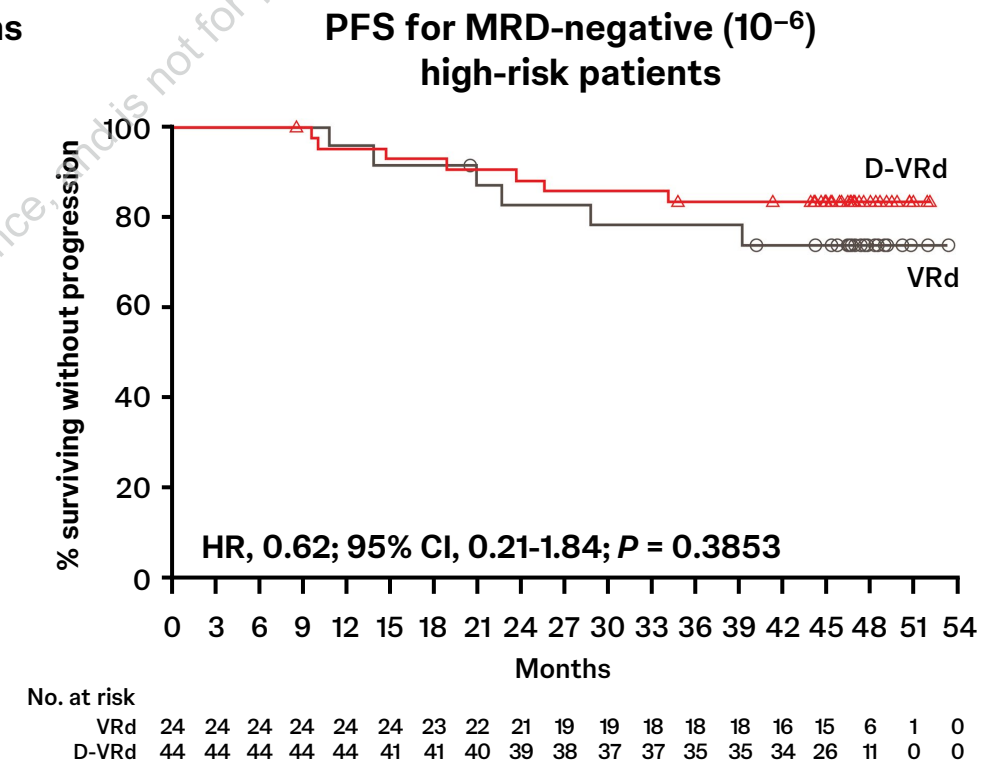
MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. The subgroup analysis for type of MM was performed on data from patients who had measurable disease in serum. Cytogenetic risk was assessed by fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

Presented by P Sonneveld at the European Hematology Association (EHA) Hybrid Congress; June 13-16, 2024; Madrid, Spain

PERSEUS: MRD Negativity in Patients With High-risk MM (ITT)







- **Rates of MRD negativity at 10^{-6} and sustained MRD negativity ≥12 months were approximately doubled with D-VRd versus VRd**
- **PFS was improved with D-VRd versus VRd in MRD-negative high-risk patients**

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. Cytogenetic risk was assessed by fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

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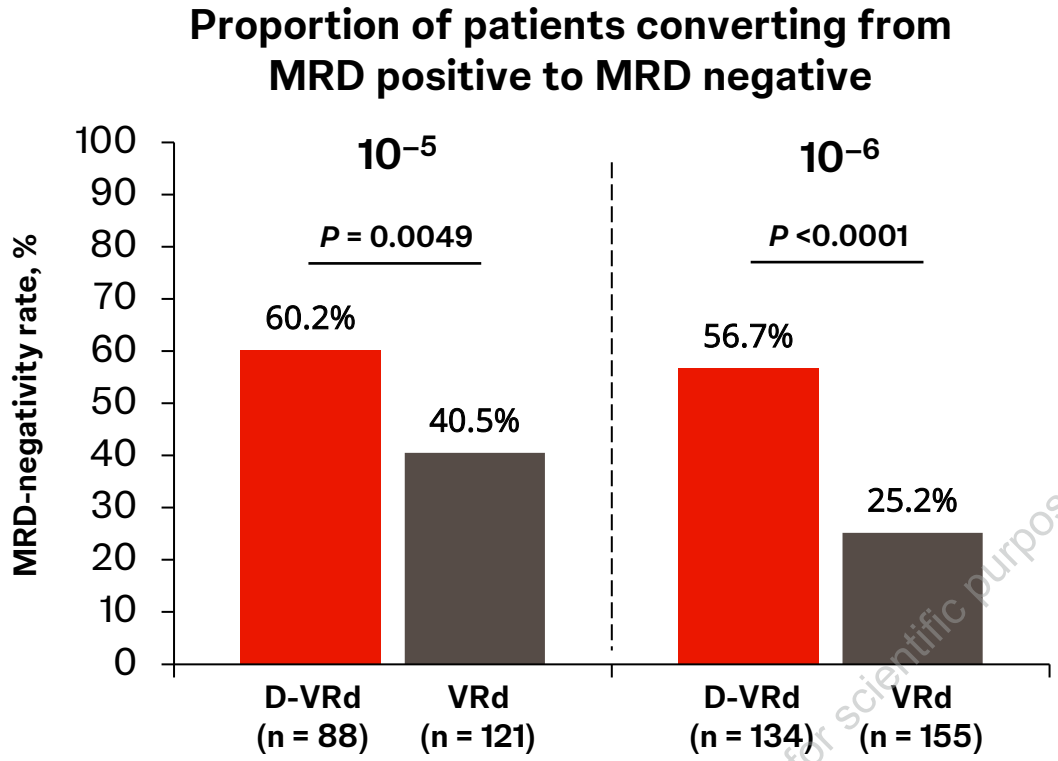
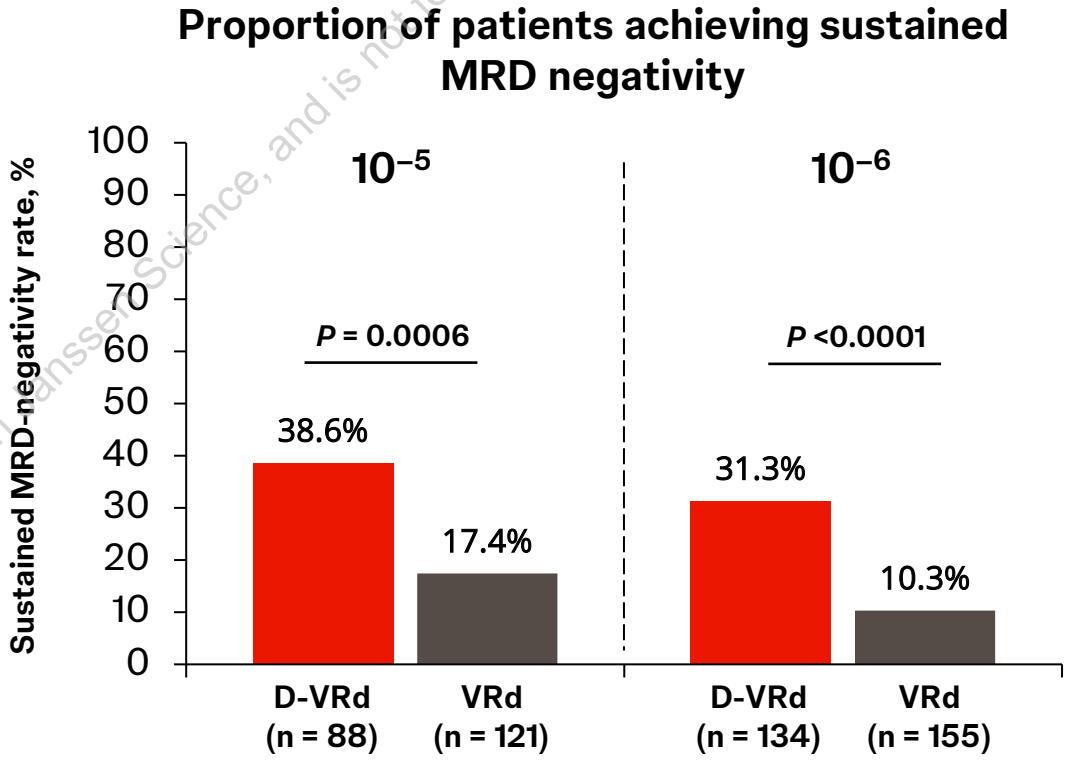
PERSEUS: MRD Conversion During Maintenance for Patients Remaining MRD Positive at the End of Consolidation





During maintenance, conversion to MRD negativity (10^{-6}) was doubled, and conversion to sustained MRD negativity was tripled, with D-R versus R

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. *P* values were calculated using the unstratified Cochran–Mantel–Haenszel chi-square test.

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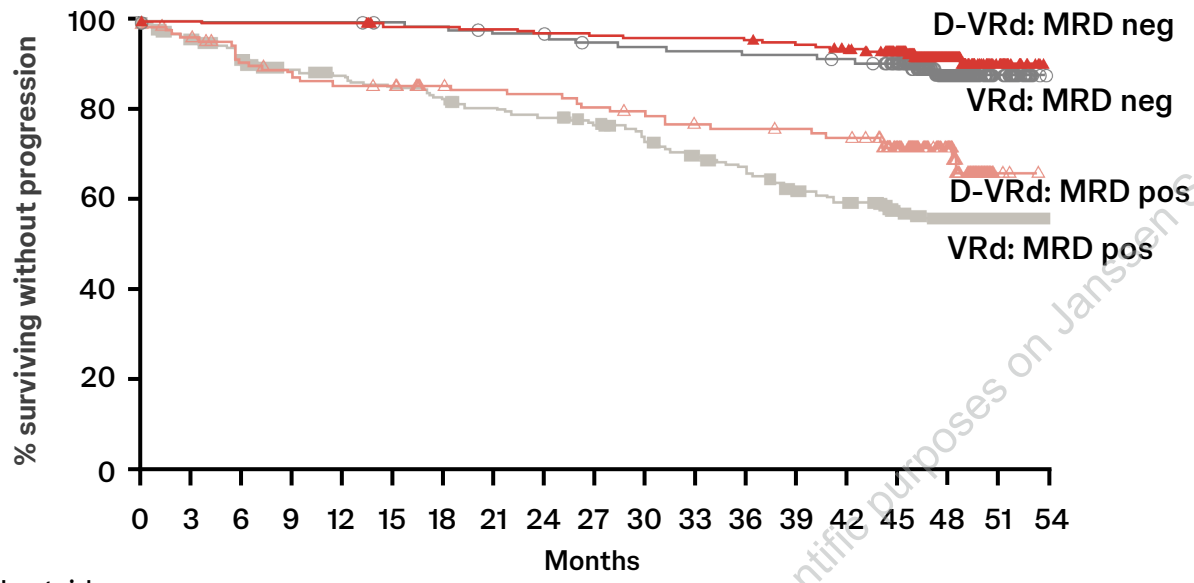
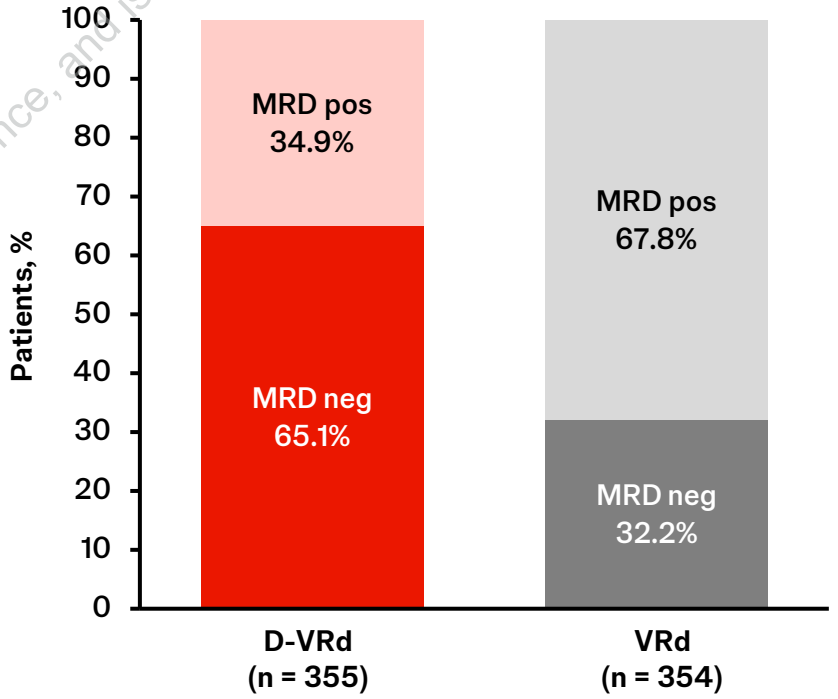
PERSEUS: PFS by MRD-negativity Status (10^{-6}; ITT)

PFS according to MRD status (10^{-6})



No. at risk																		
VRd: MRD neg	114	114	114	114	114	112	111	108	107	104	103	102	101	101	98	87	34	9	0
D-VRd: MRD neg	231	231	230	230	230	226	226	225	223	222	221	221	219	216	210	169	70	10	0
VRd: MRD pos	240	221	207	197	190	185	180	175	171	166	155	145	137	127	121	88	33	4	0
D-VRd: MRD pos	124	114	105	99	97	96	92	91	90	87	84	81	80	79	76	57	20	1	0

Overall MRD negativity (10^{-6})



- **MRD negativity at 10^{-6} was associated with improved long-term outcomes**
- **Twice as many patients achieved MRD negativity at 10^{-6} with D-VRd + D-R versus VRd + R**
- **Patients remaining MRD positive had improved PFS with D-R maintenance versus R alone**

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive.

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PERSEUS: Conclusions From Analysis of MRD

- **The potential for a cure in NDMM is predicated on reaching sustained MRD negativity at 10^{-6}**

- **In the PERSEUS study, for D-VRd + D-R:**
  - 47% of patients achieved sustained MRD negativity (10^{-6}) for 12 months versus 19% with VRd + R
  - In high-risk patients: 58% of patients achieved MRD negativity (10^{-6}) and 30% achieved sustained MRD negativity (10^{-6}) versus 31% and 14%, respectively, with VRd + R

- **During D-R maintenance:**
  - The rate of MRD negativity (10^{-6}) increased by 30% versus 15% with R alone
  - 31% of MRD-positive patients converted to sustained MRD negativity (10^{-6}) versus 10% with R alone
  - 64% of patients stopped DARA after achieving sustained MRD negativity (10^{-5})[1]

These data further highlight the benefit of D-VRd and D-R maintenance as a new standard of care for transplant-eligible patients with NDMM

1. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313.

PERSEUS: Acknowledgments

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EMN

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https://www.congresshub.com/Oncology/EHA2024/Daratumumab/Sonneveld

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