Subcutaneous Daratumumab (Dara) + Bortezomib/Lenalidomide/Dexamethasone With Dara + Lenalidomide Maintenance in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma: Analysis of Sustained Minimal Residual Disease Negativity in the Phase 3 PERSEUS Trial

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Sustained MRD Negativity (10^{-5}) ≥CR in the Phase 3 PERSEUS Trial: Key Takeaways

- Rates of functionally high-risk myeloma, defined as relapse or progression within 18 months of treatment initiation, were lower than in prior frontline trials, and were halved with DVRd vs VRd
- Higher rates of sustained MRD negativity (10^{-5}) ≥CR for ≥12 and ≥24 months were achieved with DVRd induction/consolidation + DR maintenance vs VRd induction/consolidation + R maintenance
- In the nearly two-thirds of DVRd-treated patients achieving ≥12-month sustained MRD negativity (10^{-5}) ≥CR, >95% were alive and progression free at 48 months

CR, complete response; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; R, lenalidomide; VRd, bortezomib, lenalidomide, and dexamethasone.

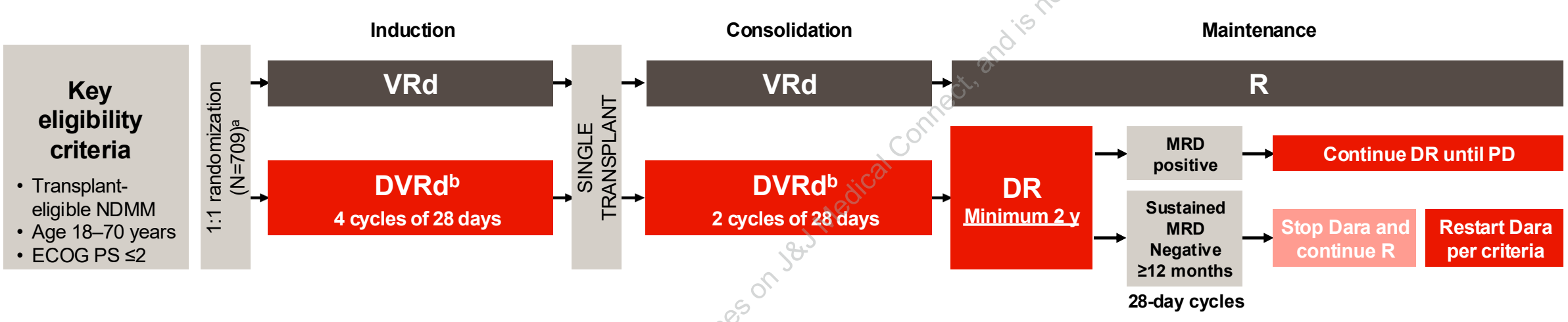
PERSEUS: Introduction

- In PERSEUS, DVRd induction/consolidation and DR maintenance improved **MRD negativity and PFS** vs VRd induction/consolidation and R maintenance[1-3]
- Functionally high-risk patients (those experiencing relapse or progression within **18 months of treatment initiation**) often have poorer survival outcomes[4,5]
- **Sustained MRD negativity**, a key efficacy endpoint and prognostic marker, is linked to improved survival[6-8]
- This post hoc analysis explored 2 distinct aims in PERSEUS:
  - **Aim 1:** To determine whether DVRd + DR maintenance reduces the number of functionally high-risk patients
  - **Aim 2:** To explore the impact of sustained MRD negativity (10^{-5}) ≥CR on PFS

CR, complete response; DR, daratumumab and lenalidomide; DRd, daratumumab, lenalidomide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; DVTd, daratumumab, bortezomib, thalidomide, and dexamethasone; MRD, minimal residual disease; PFS, progression-free survival; R, lenalidomide; VRd, bortezomib, lenalidomide, and dexamethasone.

1. ClinicalTrial.gov Identifier: NCT03710603. 2. Sonneveld P, et al. *N Engl J Med* 2024;390:301-13. 3. Rodriguez-Otero P, et al. Presented at ASCO; May 31–June 4, 2024; Chicago, IL, USA & VIrtual. 4. Gay F, et al. *Hematology* 2023;2023:433-42. 5. Rees MJ, Kumar S. *Am J Hematol* 2024;99:1560-75. 6. Mateos MV, et al. *Haematologica* 2021;106:2556-68. 7. Cavo M, et al. *Blood* 2022;139:835-44. 8. Wang J, et al. *Discov Oncol* 2024;15:38.

PERSEUS: Study Design

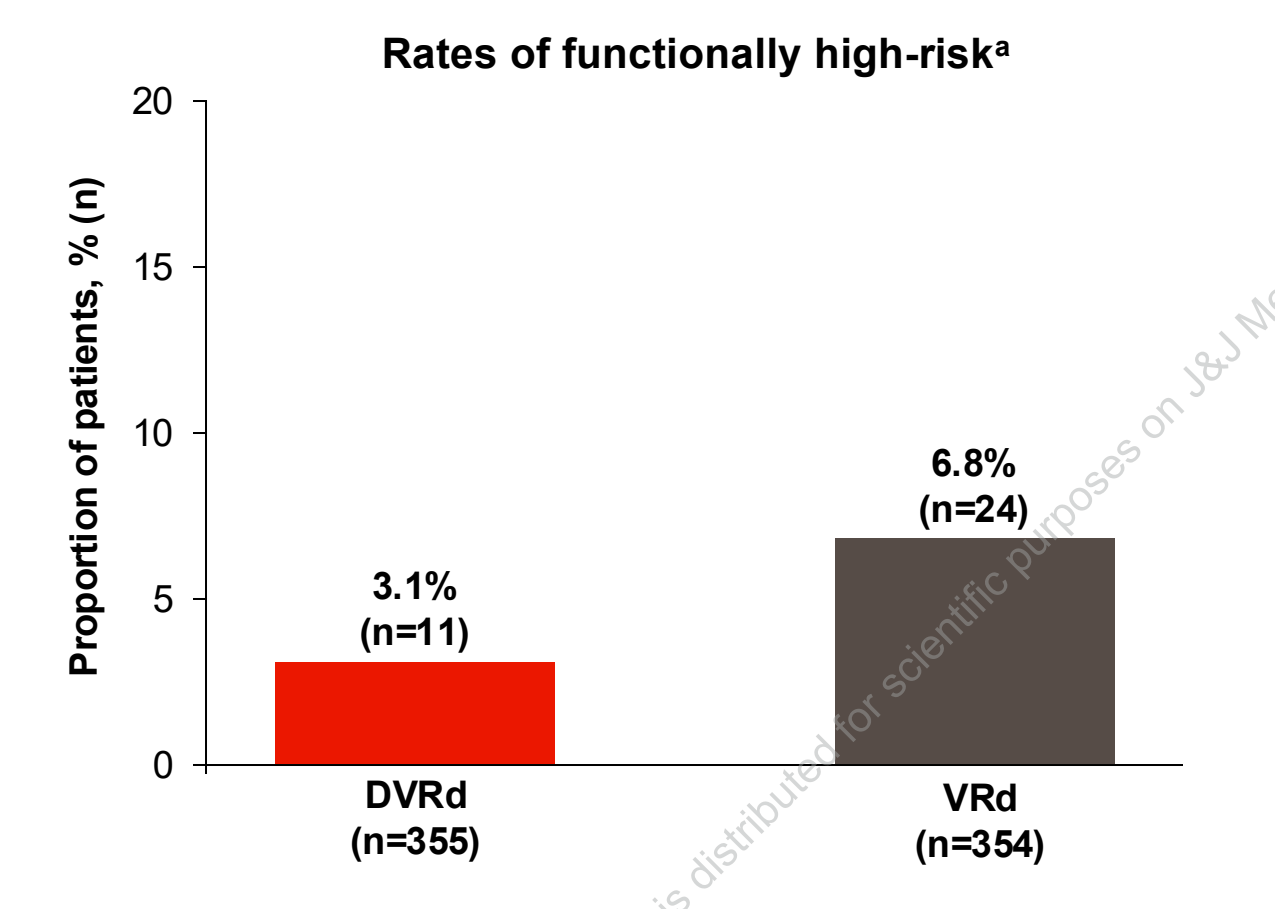


- MRD-negativity[c] rate was defined as the proportion of patients achieving MRD negativity and ≥CR in the ITT population
  - Patients who were not evaluable or had indeterminate results were considered MRD positive
  - MRD was evaluated post consolidation[d] at the time of suspected CR/sCR; at 12, 18, 24, 30, and 36 months after cycle 1 day 1; and yearly thereafter[e]

[a]Stratified by ISS stage and cytogenetic risk. [b]Dara 1800 mg co-formulated with rHuPH20 (2000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA); VRd administered as in the VRd group. [c]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. [d]In patients with ≥VGPR. [e]In patients who achieved CR/sCR and remained on study.

CR, complete response; Dara, daratumumab; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; ITT, intent-to-treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; rHuPH20, recombinant human hyaluronidase PH20; R, lenalidomide; sCR, stringent complete response; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone; y, year.

PERSEUS: Rates of Relapse or Progression Within 18 Months of Treatment Initiation (Functionally High-Risk)



Rates of functionally high-risk including preprogression deaths[b] were lower with DVRd (5.4%; n=19) vs VRd (11.0%; n=39)

Functionally high-risk[a] incidence was halved with DVRd vs VRd

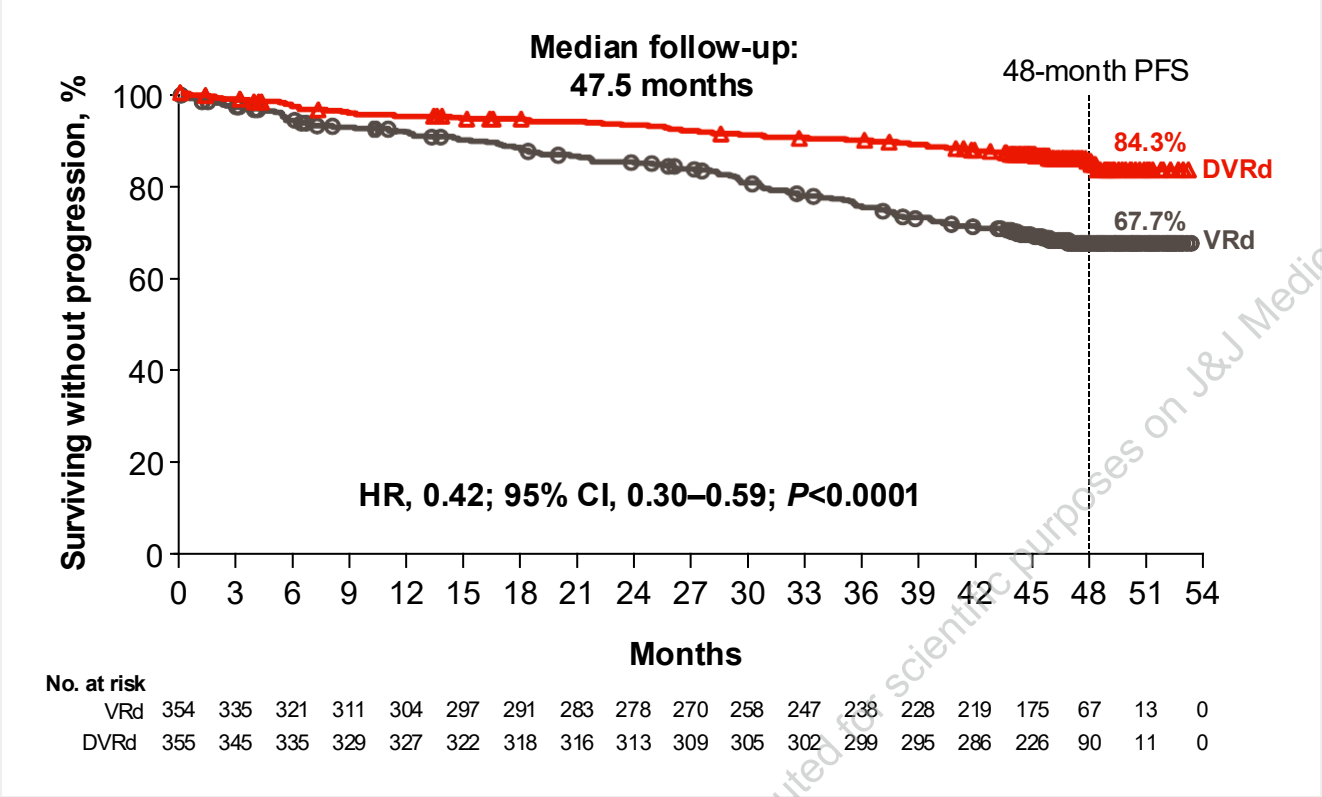
[a]Defined as those experiencing relapse or progression within 18 months of treatment initiation. [b]Defined as patients who progressed or who died within 18 months of treatment initiation.
DVRd, daratumumab and bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

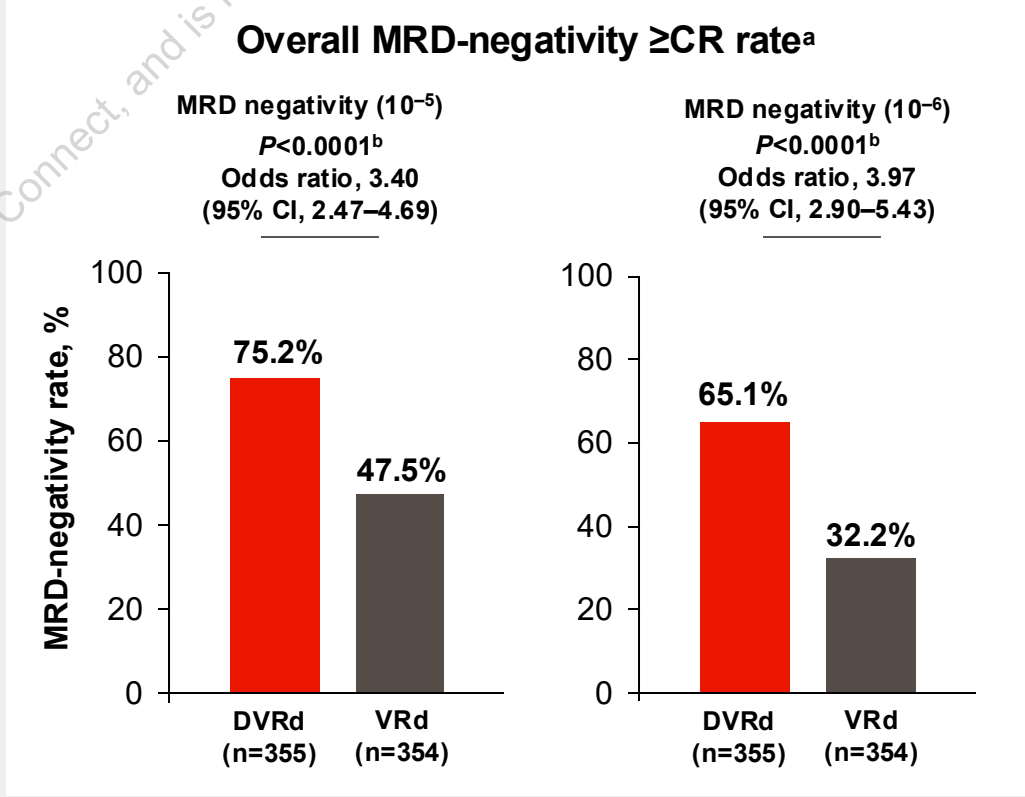
PERSEUS: Functionally High-Risk Subgroup Baseline Demographics and Clinical Characteristics

Characteristic	Functionally high-risk subgroup[a] (n=35)	ITT population (N=709)
Median age, years	60.0	60.0
ECOG PS, n (%)		
0	21 (60.0)	451 (63.6)
1	12 (34.3)	222 (31.3)
≥2	2 (5.7)	36 (5.1)
ISS staging,[b] n (%)		
I	13 (37.1)	364 (51.4)
II	13 (37.1)	239 (33.8)
III	9 (25.7)	105 (14.8)
Standard cytogenetic risk,[c] n (%)	14 (40.0)	530 (74.8)
High cytogenetic risk,[c] n (%)	20 (57.1)	154 (21.7)
del(17p)	13 (37.1)	70 (9.9)
t(4;14)	2 (5.7)	71 (10.0)
t(14;16)	7 (20.0)	25 (3.5)
CRAB criteria, n (%)	32 (91.4)	589 (83.1)

[a]Defined as those experiencing relapse or progression within 18 months of treatment initiation. [b]Based on the combination of serum β_2-microglobulin and albumin levels. [c]Based on fluorescence in situ hybridization.
CRAB, calcium, renal, anemia, bone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; ITT, intent-to-treat.

PERSEUS: DVRd and DR Maintenance Significantly Improved PFS and Overall MRD-Negativity ≥CR Rates vs VRd and R Maintenance[1]





58% reduction in the risk of progression or death in patients receiving DVRd

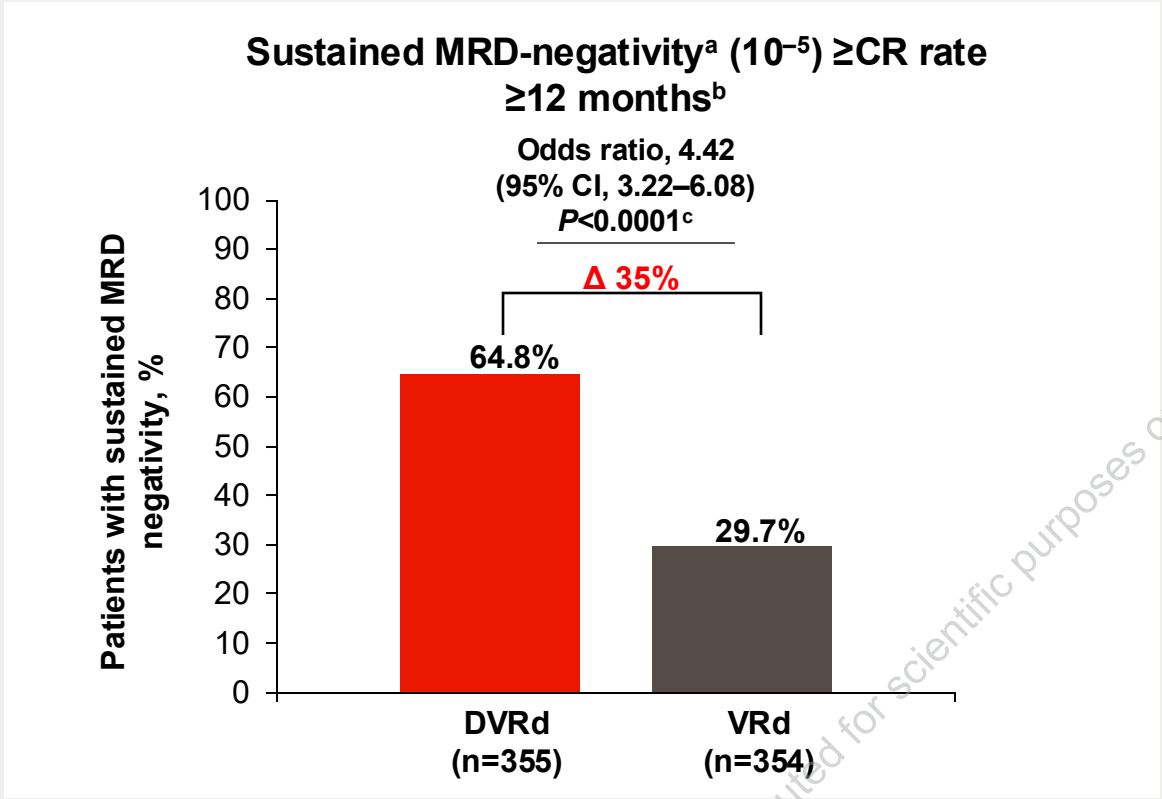
Deep and durable MRD negativity achieved with DVRd

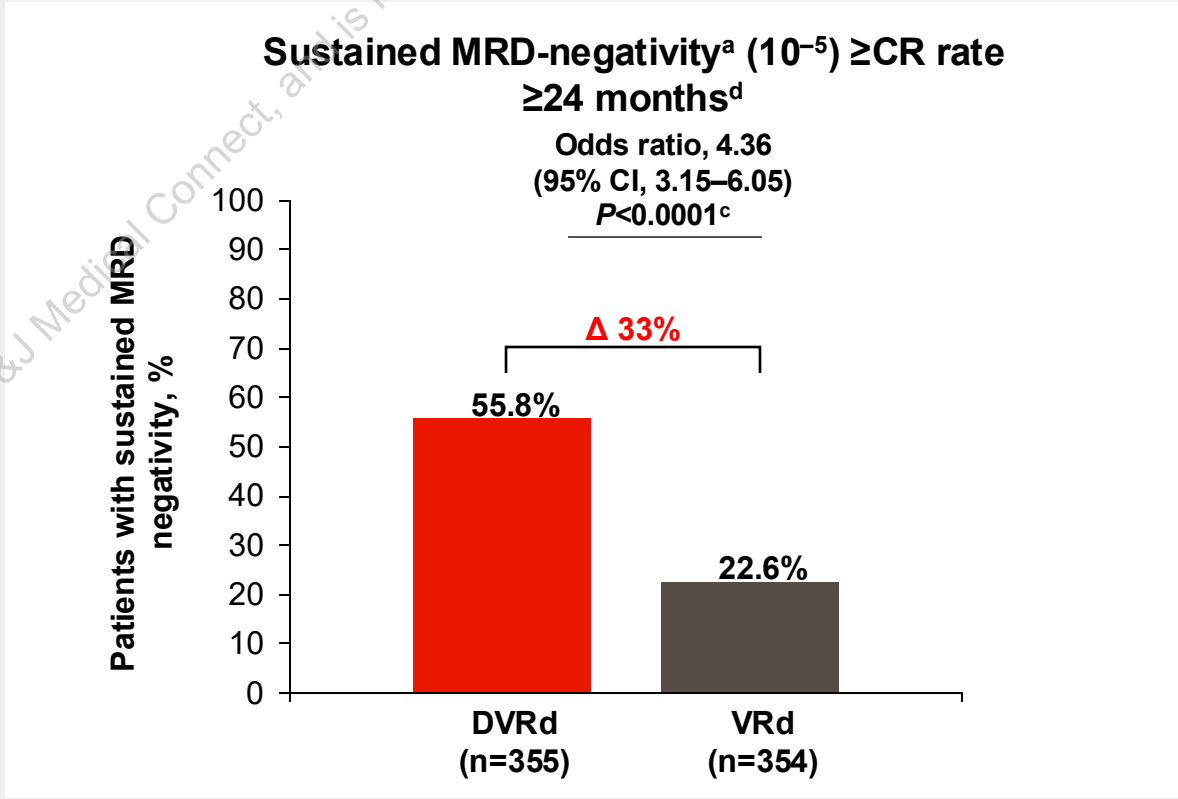
[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). [b]*P* values were calculated with the use of the stratified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

CR, complete response; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival; R, lenalidomide; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Sonneveld P, et al. *N Engl J Med* 2024;390:301-13.

PERSEUS: Sustained MRD-Negativity (10^{-5}) ≥CR Rates





DVRd more than doubled the rates of sustained MRD negativity for both ≥12 and ≥24 months vs VRd

[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]Sustained MRD negativity is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between. [c]*P* value was calculated from the stratified Cochran-Mantel-Haenszel Chi-Squared test. [d]Sustained MRD negativity is defined as 2 consecutive MRD-negative reads at least 24 months (–3) apart without MRD positive in between.
CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; NGS, next-generation sequencing; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: Sustained MRD Negativity (10^{-5}) ≥CR ≥12 Months Baseline Demographics and Clinical Characteristics

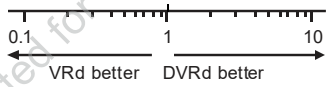
Characteristic	Sustained (≥12 mo) MRD negativity (10^{-5}) ≥CR DVRd (n=230)	Nonsustained (≥12 mo) MRD negativity (10^{-5}) ≥CR DVRd (n=125)
Median age, years	60.0	61.0
Male	131 (57.0)	80 (64.0)
ECOG PS, n (%)		
0	150 (65.2)	71 (56.8)
1	64 (27.8)	50 (40.0)
≥2	16 (6.9)	4 (3.2)
ISS staging,[a] n (%)		
I	128 (55.7)	58 (46.4)
II	69 (30.0)	45 (36.0)
III	33 (14.3)	22 (17.6)
Standard cytogenetic risk, n (%)	183 (79.6)	81 (64.8)
High cytogenetic risk,[b] n (%)	37 (16.1)	39 (31.2)
del(17p)	14 (6.1)	22 (17.6)
t(4;14)	17 (7.4)	16 (12.8)
t(14;16)	7 (3.0)	4 (3.2)

[a]Based on the combination of serum β_2-microglobulin and albumin levels. [b]Based on fluorescence in situ hybridization.
CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; MRD, minimal residual disease.

PERSEUS: Sustained MRD Negativity ≥CR by Subgroups

Sustained MRD negativity (10^{-5}) ≥CR: ≥12 months[a] ≥24 months[b]

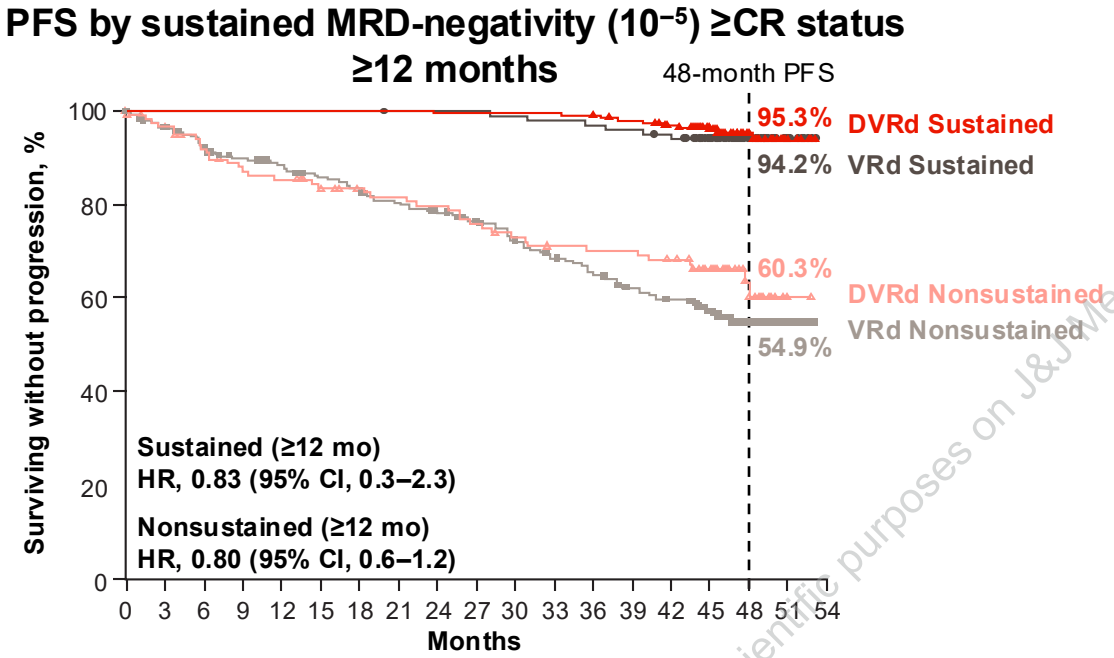
Subgroup	≥12 months[a] VRd n/N (%)	≥12 months[a] DVRd n/N (%)	≥12 months[a] Odds ratio (95% CI)	≥24 months[b] VRd n/N (%)	≥24 months[b] DVRd n/N (%)	≥24 months[b] Odds ratio (95% CI)
Sex						
Male	62/205 (30.2)	131/211 (62.1)	3.78 (2.51–5.68)	44/205 (21.5)	105/211 (49.8)	3.62 (2.36–5.57)
Female	43/149 (28.9)	99/144 (68.8)	5.42 (3.29–8.94)	30/149 (20.1)	77/144 (53.5)	4.56 (2.72–7.65)
Age						
<65 years	78/267 (29.2)	180/261 (69.0)	5.38 (3.71–7.81)	54/267 (20.2)	141/261 (54.0)	4.63 (3.15–6.81)
≥65 years	27/87 (31.0)	50/94 (53.2)	2.53 (1.37–4.64)	20/87 (23.0)	41/94 (43.6)	2.59 (1.36–4.94)
Race						
White	93/323 (28.8)	216/330 (65.5)	4.69 (3.37–6.52)	68/323 (21.1)	172/330 (52.1)	4.08 (2.89–5.76)
Other	12/31 (38.7)	14/25 (56.0)	2.02 (0.69–5.88)	6/31 (19.4)	10/25 (40.0)	2.78 (0.84–9.20)
ISS stage						
I	58/178 (32.6)	128/186 (68.8)	4.57 (2.94–7.10)	44/178 (24.7)	105/186 (56.5)	3.95 (2.52–6.17)
II	35/125 (28.0)	69/114 (60.5)	3.94 (2.29–6.78)	21/125 (16.8)	53/114 (46.5)	4.30 (2.37–7.81)
III	12/50 (24.0)	33/55 (60.0)	4.75 (2.04–11.05)	9/50 (18.0)	24/55 (43.6)	3.53 (1.44–8.65)
Type of MM						
IgG	50/185 (27.0)	136/204 (66.7)	5.40 (3.49–8.35)	35/185 (18.9)	105/204 (51.5)	4.55 (2.87–7.19)
Non-IgG	31/96 (32.3)	52/78 (66.7)	4.19 (2.22–7.92)	19/96 (19.8)	46/78 (59.0)	5.83 (2.97–11.44)
Cytogenetic risk						
Standard risk	83/266 (31.2)	183/264 (69.3)	4.98 (3.45–7.20)	58/266 (21.8)	143/264 (54.2)	4.24 (2.90–6.19)
High risk	20/78 (25.6)	37/76 (48.7)	2.75 (1.40–5.42)	14/78 (17.9)	29/76 (38.2)	2.82 (1.34–5.92)
Indeterminate	2/10 (20.0)	10/15 (66.7)	8.00 (1.21–52.69)	2/10 (20.0)	10/15 (66.7)	8.00 (1.21–52.69)
ECOG PS						
0	71/230 (30.9)	150/221 (67.9)	4.73 (3.18–7.04)	49/230 (21.3)	121/221 (54.8)	4.47 (2.96–6.75)
≥1	34/124 (27.4)	80/134 (59.7)	3.92 (2.32–6.62)	25/124 (20.2)	61/134 (45.5)	3.31 (1.90–5.76)



DVRd led to higher rates of sustained MRD negativity (10^{-5}) ≥CR vs VRd across subgroups

 [b]Sustained MRD negativity is defined as 2 consecutive MRD-negative reads at least 24-months (–3) apart without MRD positive in between. 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). CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; Ig, immunoglobulin; ISS, International Staging System; ITT, intent-to-treat; MM, multiple myeloma; MRD, minimal residual disease; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: PFS by Sustained MRD-Negativity (10^{-5}) ≥CR Status at ≥12 months



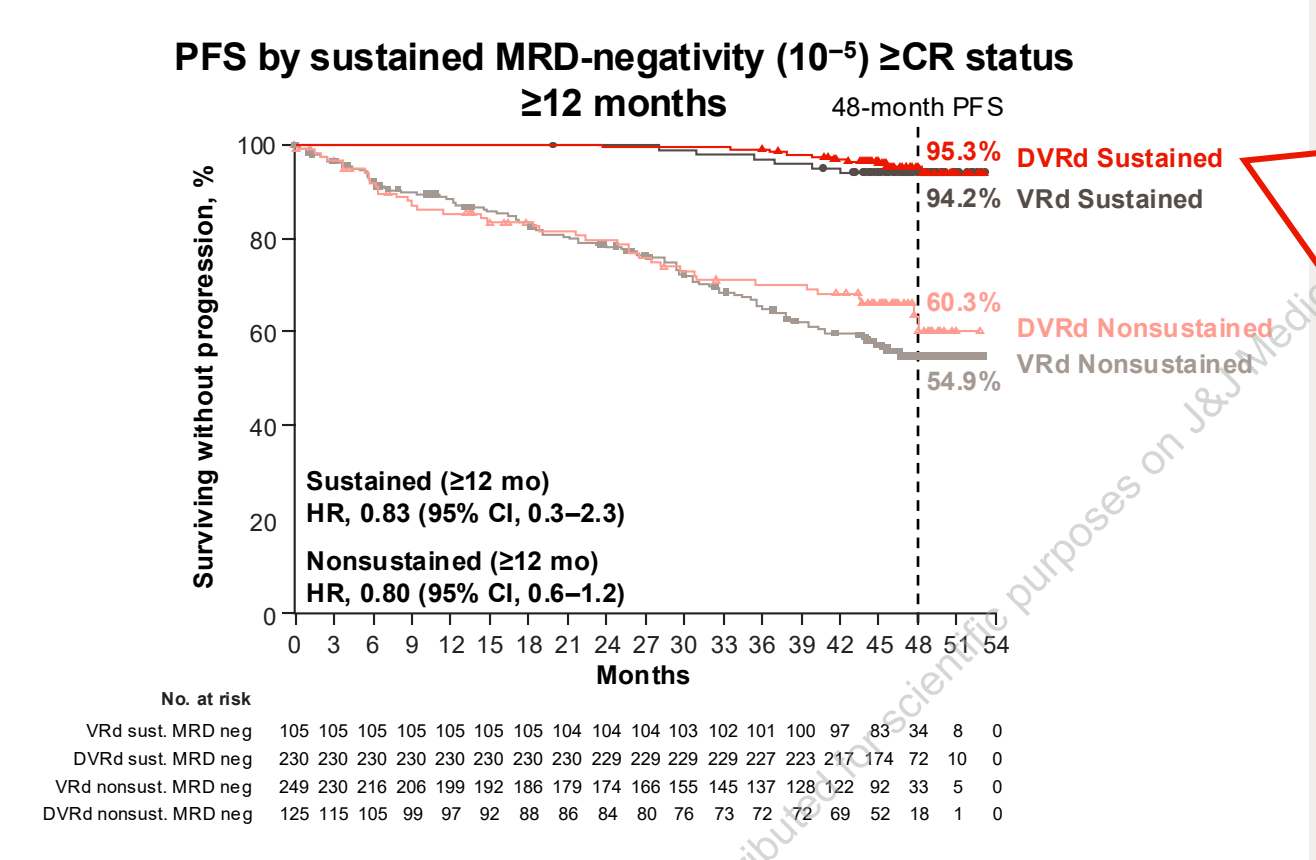
No. at risk

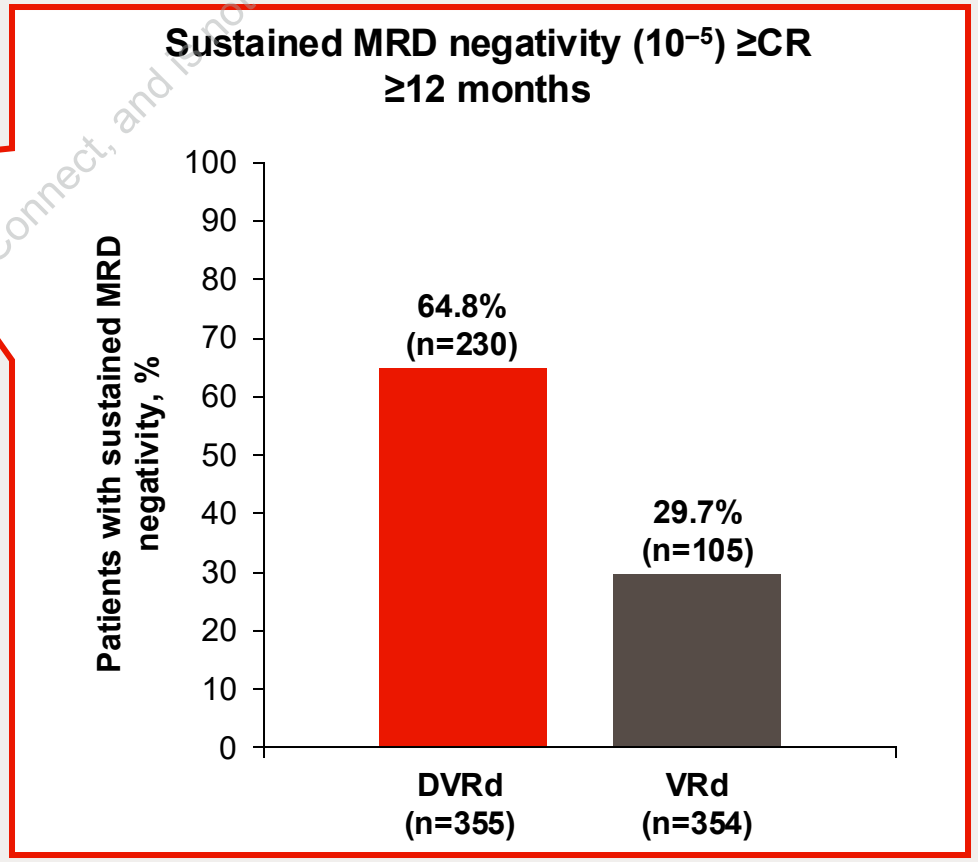
VRd sust. MRD neg	105	105	105	105	105	105	105	104	104	104	103	102	101	100	97	83	34	8	0
DVRd sust. MRD neg	230	230	230	230	230	230	230	230	229	229	229	229	227	223	217	174	72	10	0
VRd nonsust. MRD neg	249	230	216	206	199	192	186	179	174	166	155	145	137	128	122	92	33	5	0
DVRd nonsust. MRD neg	125	115	105	99	97	92	88	86	84	80	76	73	72	72	69	52	18	1	0

- Sustained MRD-negativity (10^{-5}) ≥CR rates for ≥12 months were twice as high with DVRd vs VRd
- Among these patients, 48-month PFS rates were ~95% in both arms

CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; mo, month; MRD, minimal residual disease; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: PFS by Sustained MRD-Negativity (10^{-5}) ≥CR Status at ≥12 months





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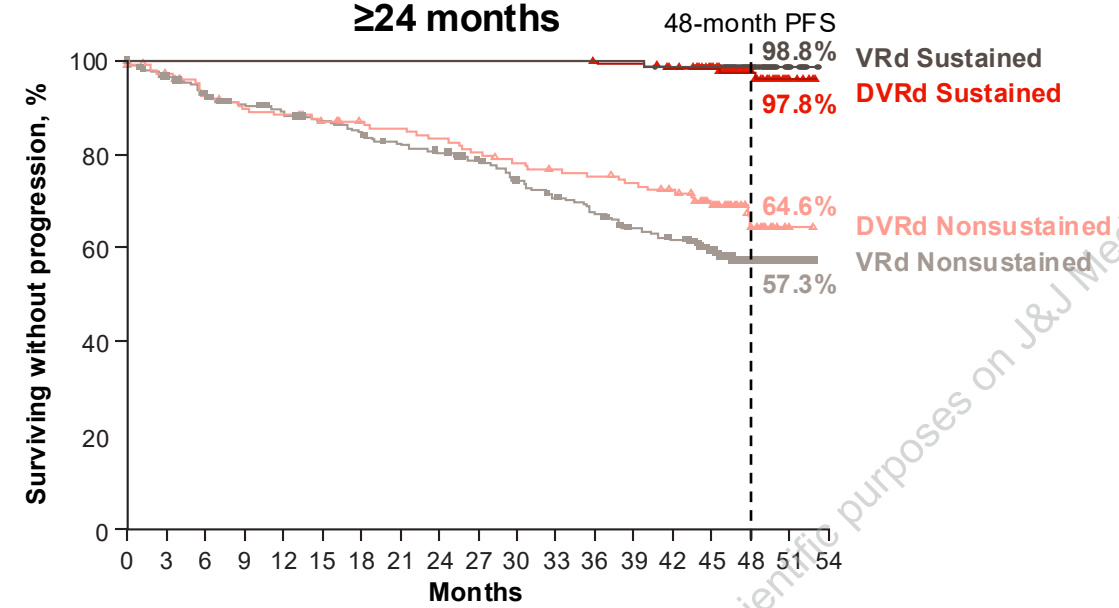
PERSEUS: PFS by Sustained MRD-Negativity (10^{-5}) ≥CR Status at ≥24 months



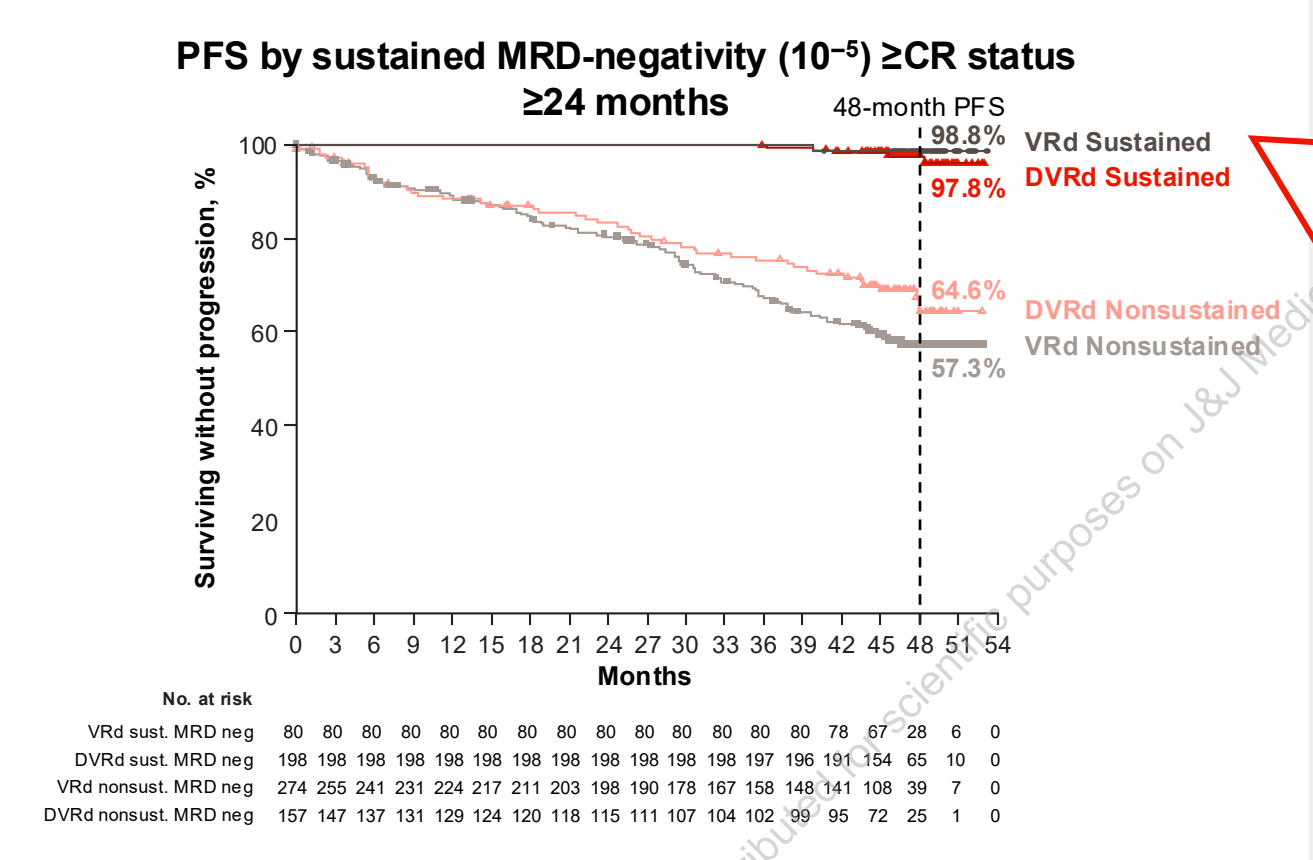
No. at risk

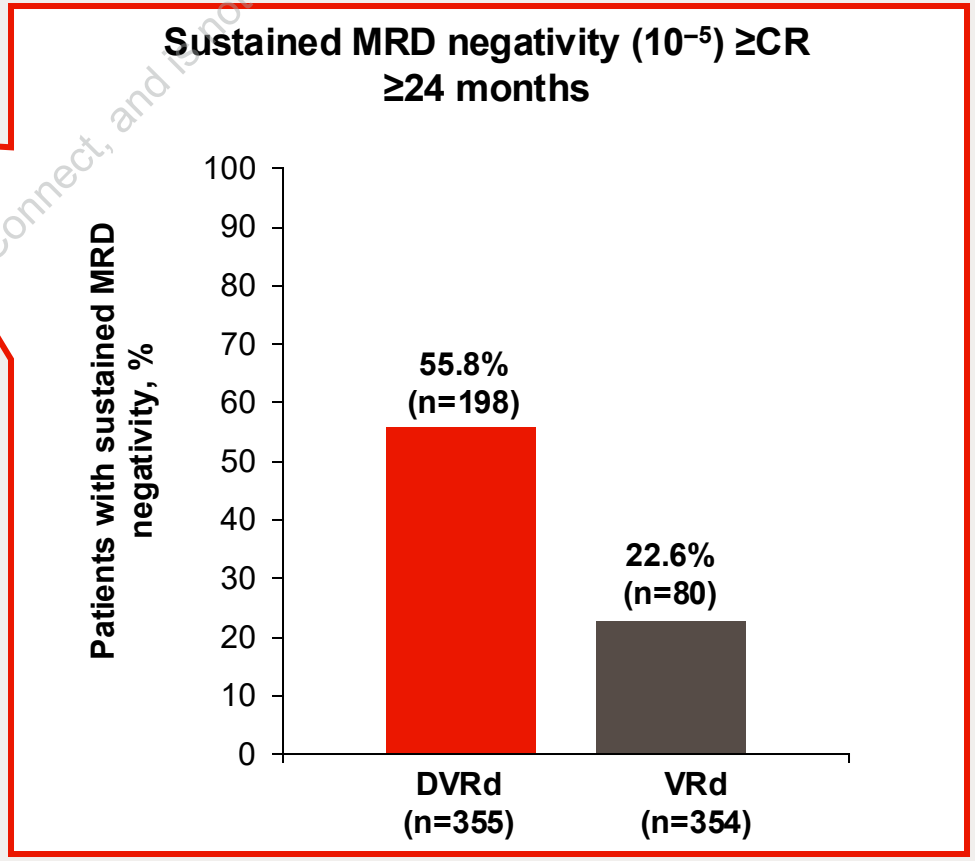
VRd sust. MRD neg	80	80	80	80	80	80	80	80	80	80	80	80	80	78	67	28	6	0
DVRd sust. MRD neg	198	198	198	198	198	198	198	198	198	198	198	198	197	196	191	154	65	10	0
VRd nonsust. MRD neg	274	255	241	231	224	217	211	203	198	190	178	167	158	148	141	108	39	7	0
DVRd nonsust. MRD neg	157	147	137	131	129	124	120	118	115	111	107	104	102	99	95	72	25	1	0

- **Sustained MRD-negativity (10^{-5}) ≥CR rates for ≥24 months were more than twice as high with DVRd vs VRd**
- **Among these patients, 48-month PFS rates exceeded 95% in both arms**

CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: PFS by Sustained MRD-Negativity (10^{-5}) ≥CR Status at ≥24 months





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CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.

Sustained MRD Negativity in the Phase 3 PERSEUS Trial: Conclusions

- Rates of relapse or progression **within 18 months** of treatment initiation (functionally high-risk disease) were lower than seen in other frontline trials[1] and were halved with **DVRd** (**3.1%**; n=11) vs VRd (6.8%; n=24)
- DVRd + DR maintenance led to deeper and more durable responses, and was associated with improved PFS
  - **Higher rates of sustained MRD negativity** (10^{-5}) ≥CR were achieved with DVRd vs VRd, with nearly two-thirds of patients achieving sustained MRD negativity for ≥12 months and more than half achieving sustained MRD negativity for ≥24 months
  - **Sustained MRD negativity** was associated with a **PFS benefit**, with **>95%** of patients with ≥12- or ≥24-month sustained MRD negativity remaining progression free at 48 months

These results reinforce the consistent benefit of DVRd + DR maintenance and further support the PERSEUS regimen as SOC for TE NDMM

CR, complete response; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; SOC, standard of care; TE, transplant-eligible; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Gay F, et al. *Hematology* 2023;2023:433-42.

PERSEUS: Acknowledgments

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