Daratumumab + Bortezomib, Lenalidomide, and Dexamethasone (VRd) Versus VRd Alone in Patients With Newly Diagnosed Multiple Myeloma Ineligible for SCT or for Whom SCT is Not Planned as Initial Therapy: Analysis of Minimal Residual Disease in the Phase 3 CEPHEUS Trial

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CEPHEUS: Introduction

- MRD negativity is associated with longer survival and is a strong prognostic clinical endpoint in MM[1-3]
- MRD negativity was supported by a unanimous ODAC vote as an early endpoint for accelerated approval in MM[4]
- Daratumumab (DARA) frontline regimens have demonstrated improved depth and duration of response leading to improved PFS in five phase 3 trials: CEPHEUS,[5] PERSEUS,[6] CASSIOPEIA,[7] MAIA,[8] and ALCYONE[9]
- CEPHEUS,[5] the first phase 3 DARA study with MRD as a primary endpoint, showed that the addition of DARA SC to VRd in TIE or transplant-deferred patients with NDMM:
  - Led to superior rates of overall and sustained MRD negativity ≥CR, and rates of ≥CR
  - Significantly improved PFS versus VRd (HR, 0.57; *P* = 0.0005)

Here we report an expanded analysis of MRD outcomes from CEPHEUS

MRD, minimal/measurable residual disease; MM, multiple myeloma; ODAC, Oncologic Drugs Advisory Committee; PFS, progression-free survival; SC, subcutaneous; VRd, bortezomib/lenalidomide/dexamethasone; TIE, transplant-ineligible; NDMM, newly diagnosed multiple myeloma; CR, complete response; HR, hazard ratio; IMS, International Myeloma Society. 1. Munshi NC, et al. *Blood Adv*. 2020;4(23):5988-5999. 2. Perrot A, et al. *Blood*. 2018;132(23):2456-2464. 3. San-Miguel J, et al. *Blood*. 2022;139(4):492-501. 4. International Myeloma Foundation. https://www.myeloma.org/blog/dr-duries/odac-unanimously-in-favor-mrd-testing-early-endpoint-myeloma. Published 18 April 2024. Accessed 14 June 2024. 5. Usmani SZ, et al. Presented at the 21st IMS Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. 6. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313. 7. Moreau P, et al. *Lancet Oncol*. 2024;25(8):1003-1014. 8. Facon T, et al. *Lancet Oncol*. 2021;22(11):1582-1596. 9. Mateos MV, et al. *Lancet*. 2020;395(10218):132-141.

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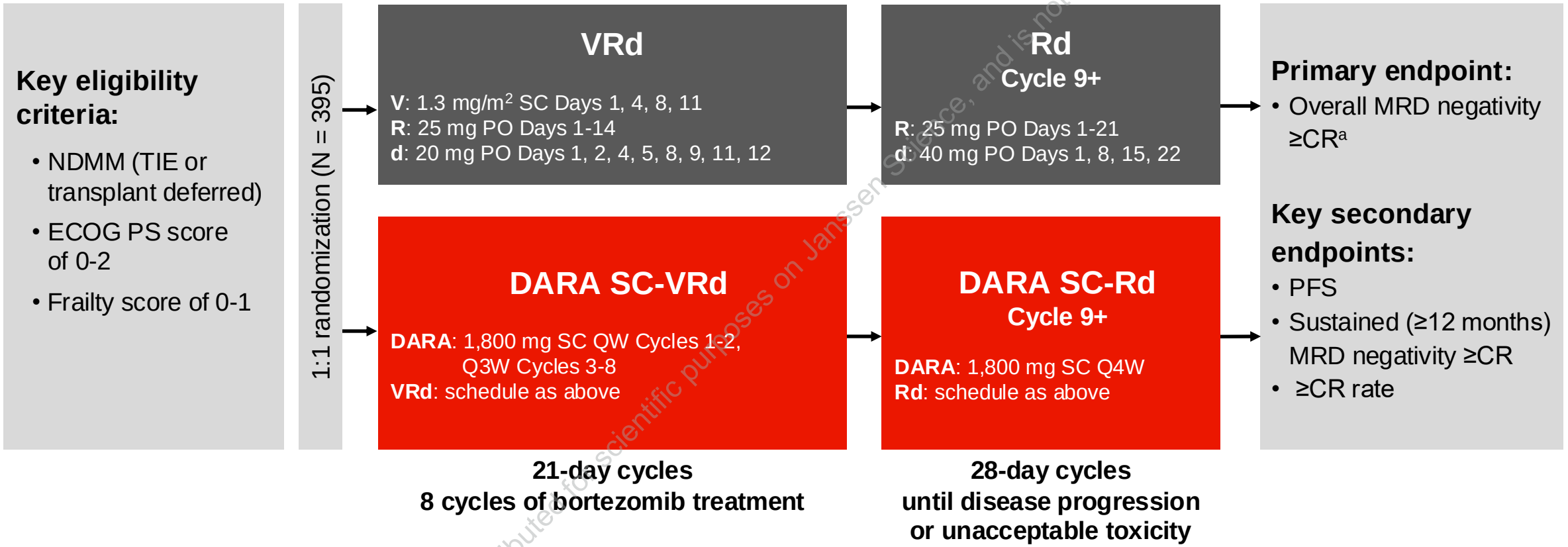
CEPHEUS: Study Design



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 not in CR were considered MRD positive.

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; R, lenalidomide; PO, oral; d, dexamethasone; DARA SC (DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA]); QW, weekly; Q3W, every 3 weeks; Q4W, every 4 weeks; Rd, lenalidomide/dexamethasone; ITT, intent-to-treat. [a]MRD was assessed via next-generation sequencing (clonoSEQ®; Adaptive Biotechnologies) using bone marrow aspirate samples obtained at baseline, at the time of suspected CR, and at 12, 18, 24, 30, and 36 months after the first dose and annually thereafter in patients with CR. ClinicalTrials.gov Identifier: NCT03652064. Accessed October 7, 2024.

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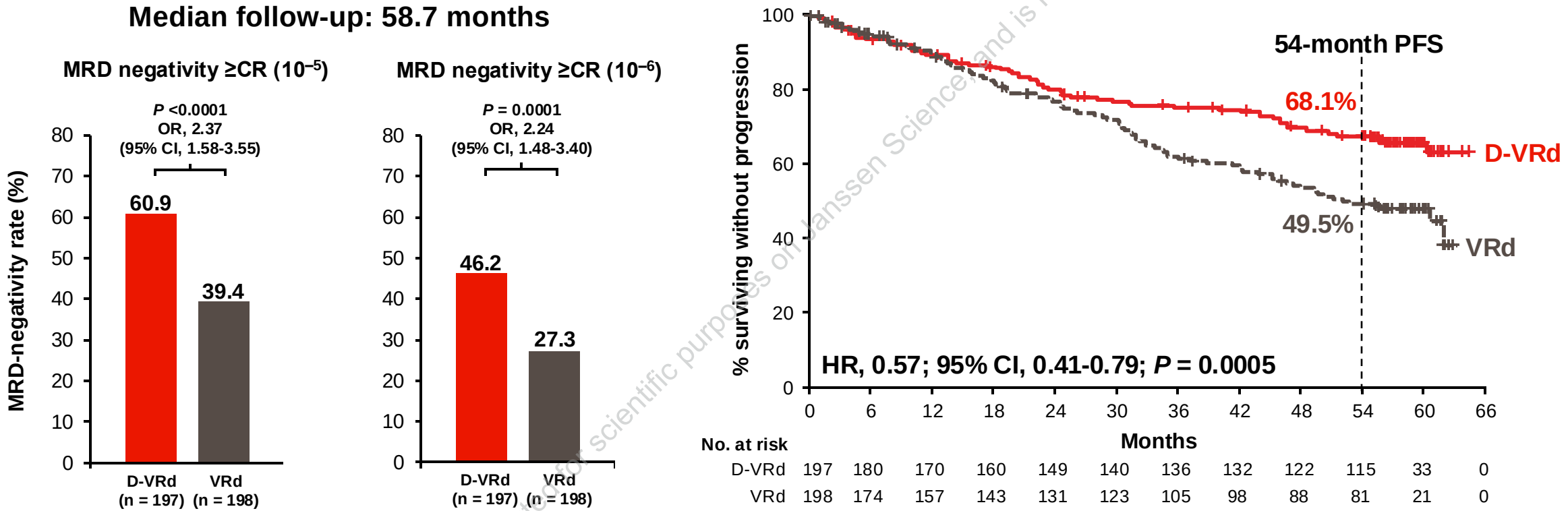
CEPHEUS: Primary Endpoint of Overall MRD-negativity ≥CR (10^{-5} and 10^{-6}) Rates and PFS[1]



Adding daratumumab to VRd led to ~50% increase in MRD-negativity ≥CR rates versus VRd alone

Daratumumab significantly improved PFS, with a 43% reduction in the risk of disease progression or death

OR, odds ratio; CI, confidence interval; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone.

1. Usmani SZ, et al. Presented at the 21st IMS Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil.

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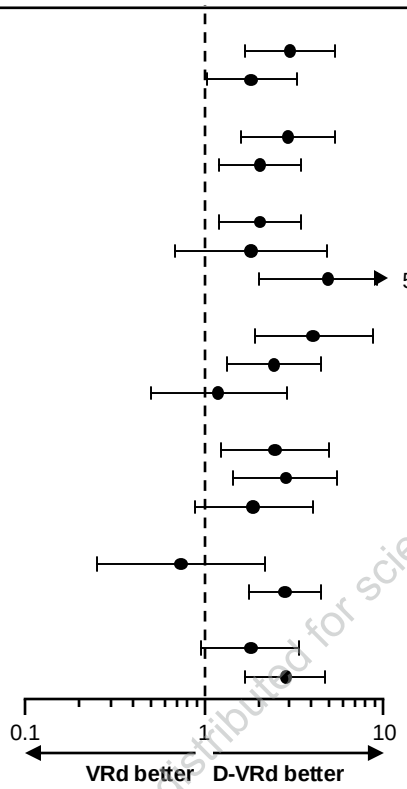
CEPHEUS: MRD-negativity ≥CR (10^{-5} and 10^{-6}) Rates in Prespecified Subgroups

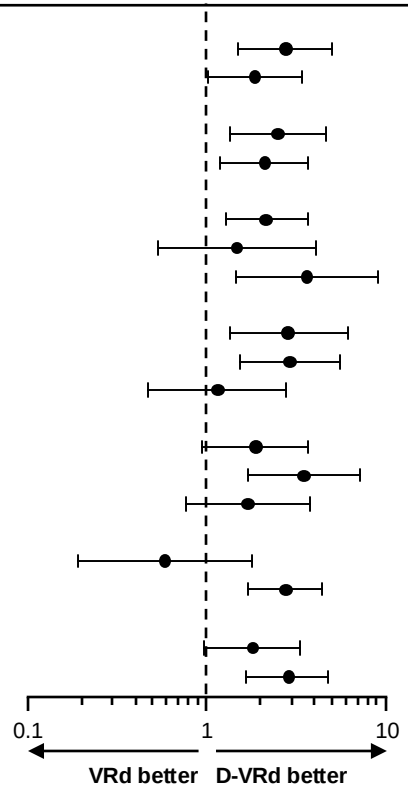
MRD negativity ≥CR (10^{-5})

Subgroup	D-VRd n/N (%)	VRd n/N (%)	Odds ratio[a] (95% CI)
Sex			
Male	54/87 (62.1)	39/111 (35.1)	3.02 (1.69-5.41)
Female	66/110 (60.0)	39/87 (44.8)	1.85 (1.04-3.26)
Age			
<70 years	59/88 (67.0)	36/88 (40.9)	2.94 (1.59-5.44)
≥70 years	61/109 (56.0)	42/110 (38.2)	2.06 (1.20-3.53)
Region			
Europe	69/120 (57.5)	46/116 (39.7)	2.06 (1.23-3.46)
North America	21/37 (56.8)	13/31 (41.9)	1.82 (0.69-4.77)
Other	30/40 (75.0)	19/51 (37.3)	5.05 (2.03-12.60)
Weight			
≤65 kg	40/58 (69.0)	22/63 (34.9)	4.14 (1.94-8.86)
>65-85 kg	58/101 (57.4)	31/88 (35.2)	2.48 (1.38-4.47)
>85 kg	22/38 (57.9)	25/47 (53.2)	1.21 (0.51-2.87)
ISS disease stage			
I	45/68 (66.2)	30/68 (44.1)	2.48 (1.24-4.96)
II	47/73 (64.4)	29/75 (38.7)	2.87 (1.47-5.59)
III	28/56 (50.0)	19/55 (34.5)	1.89 (0.88-4.07)
Cytogenetic risk			
High risk[b]	12/25 (48.0)	15/27 (55.6)	0.74 (0.25-2.20)
Standard risk	95/149 (63.8)	57/149 (38.3)	2.84 (1.78-4.54)
ECOG PS score			
0	41/71 (57.7)	36/84 (42.9)	1.82 (0.96-3.45)
≥1	79/126 (62.7)	42/114 (36.8)	2.88 (1.71-4.87)



MRD negativity ≥CR (10^{-6})

Subgroup	D-VRd n/N (%)	VRd n/N (%)	Odds ratio[a] (95% CI)
Sex			
Male	42/87 (48.3)	28/111 (25.2)	2.77 (1.52-5.04)
Female	49/110 (44.5)	26/87 (29.9)	1.88 (1.04-3.41)
Age			
<70 years	44/88 (50.0)	25/88 (28.4)	2.52 (1.35-4.70)
≥70 years	47/109 (43.1)	29/110 (26.4)	2.12 (1.20-3.74)
Region			
Europe	57/120 (47.5)	34/116 (29.3)	2.18 (1.28-3.73)
North America	14/37 (37.8)	9/31 (29.0)	1.49 (0.54-4.13)
Other	20/40 (50.0)	11/51 (21.6)	3.64 (1.46-9.04)
Weight			
≤65 kg	31/58 (53.4)	18/63 (28.6)	2.87 (1.35-6.09)
>65-85 kg	45/101 (44.6)	19/88 (21.6)	2.92 (1.54-5.54)
>85 kg	15/38 (39.5)	17/47 (36.2)	1.15 (0.48-2.78)
ISS disease stage			
I	32/68 (47.1)	22/68 (32.4)	1.86 (0.93-3.73)
II	37/73 (50.7)	17/75 (22.7)	3.51 (1.73-7.13)
III	22/56 (39.3)	15/55 (27.3)	1.73 (0.78-3.84)
Cytogenetic risk			
High risk[b]	8/25 (32.0)	12/27 (44.4)	0.59 (0.19-1.83)
Standard risk	71/149 (47.7)	37/149 (24.8)	2.76 (1.69-4.50)
ECOG PS score			
0	28/71 (39.4)	27/84 (32.1)	1.37 (0.71-2.66)
≥1	63/126 (50.0)	27/114 (23.7)	3.22 (1.85-5.61)



Daratumumab benefit was generally consistent across prespecified subgroups

FISH, fluorescence in situ hybridization. [a]Mantel-Haenszel estimate of the common odds ratio for unstratified tables is used. An odds ratio >1 indicates an advantage for D-VRd. [b]High risk was defined as the presence of del(17p), t(4;14), and/or t(14;16), as assessed by FISH testing.

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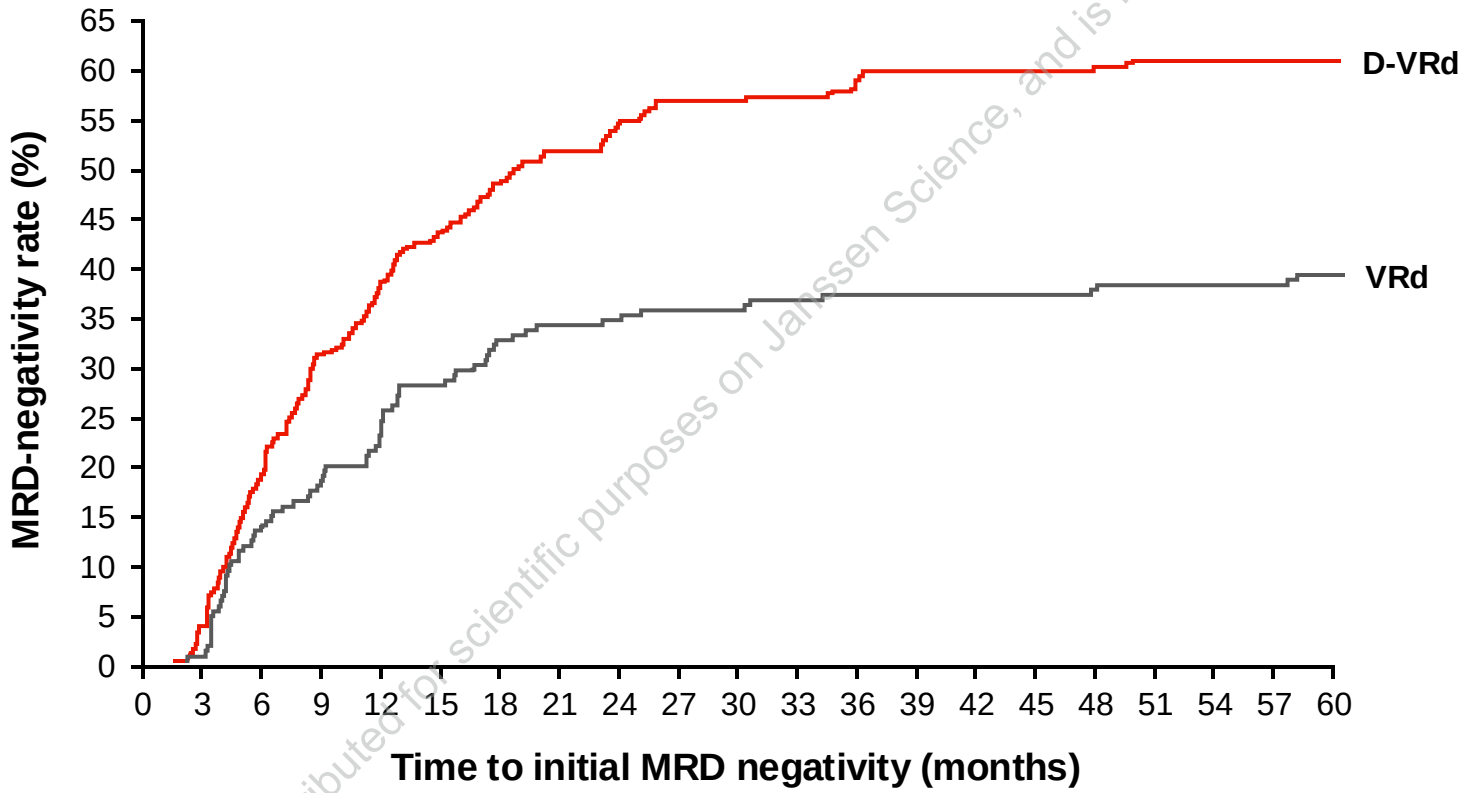
CEPHEUS: Cumulative MRD-negativity ≥CR (10^{-5}) Rate Over Time



- The addition of daratumumab to VRd led to faster attainment of MRD negativity ≥CR
- MRD-negativity ≥CR rates continued to improve over time with D-VRd versus VRd

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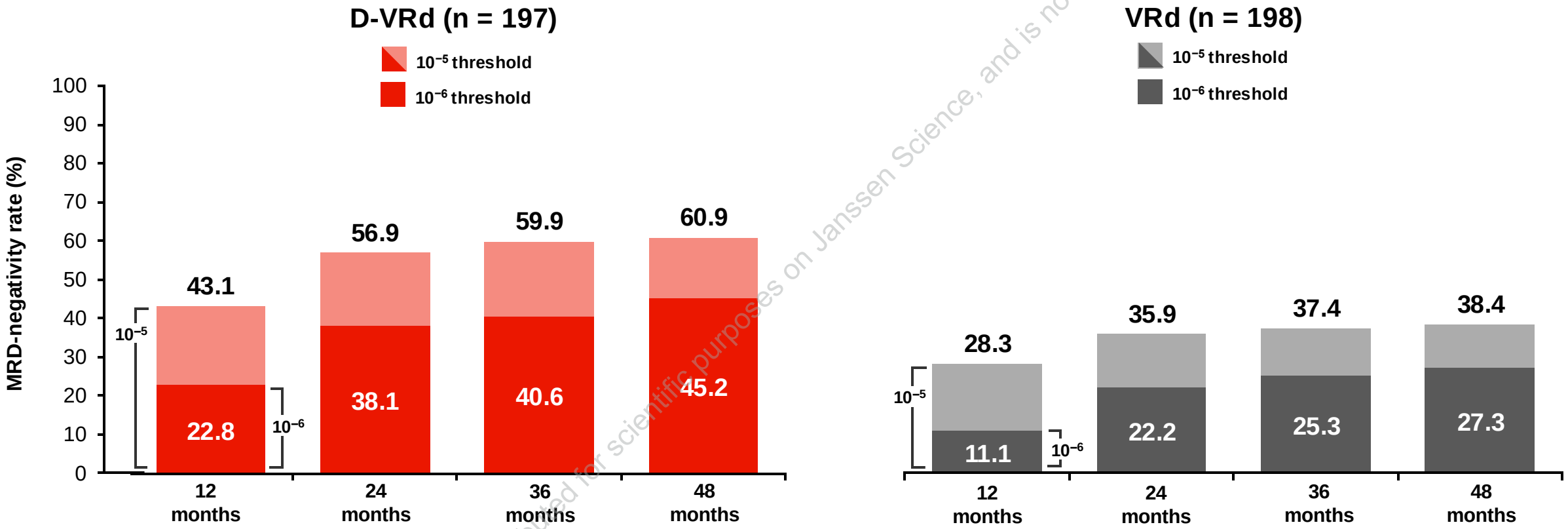
CEPHEUS: Cumulative MRD-negativity ≥CR (10^{-5} and 10^{-6}) Rates



The addition of daratumumab to VRd improved cumulative MRD-negativity ≥CR rates versus VRd at all prespecified time points at both 10^{-5} and 10^{-6}

A window of ±3 months at each time point was applied to complete the bone marrow aspiration.

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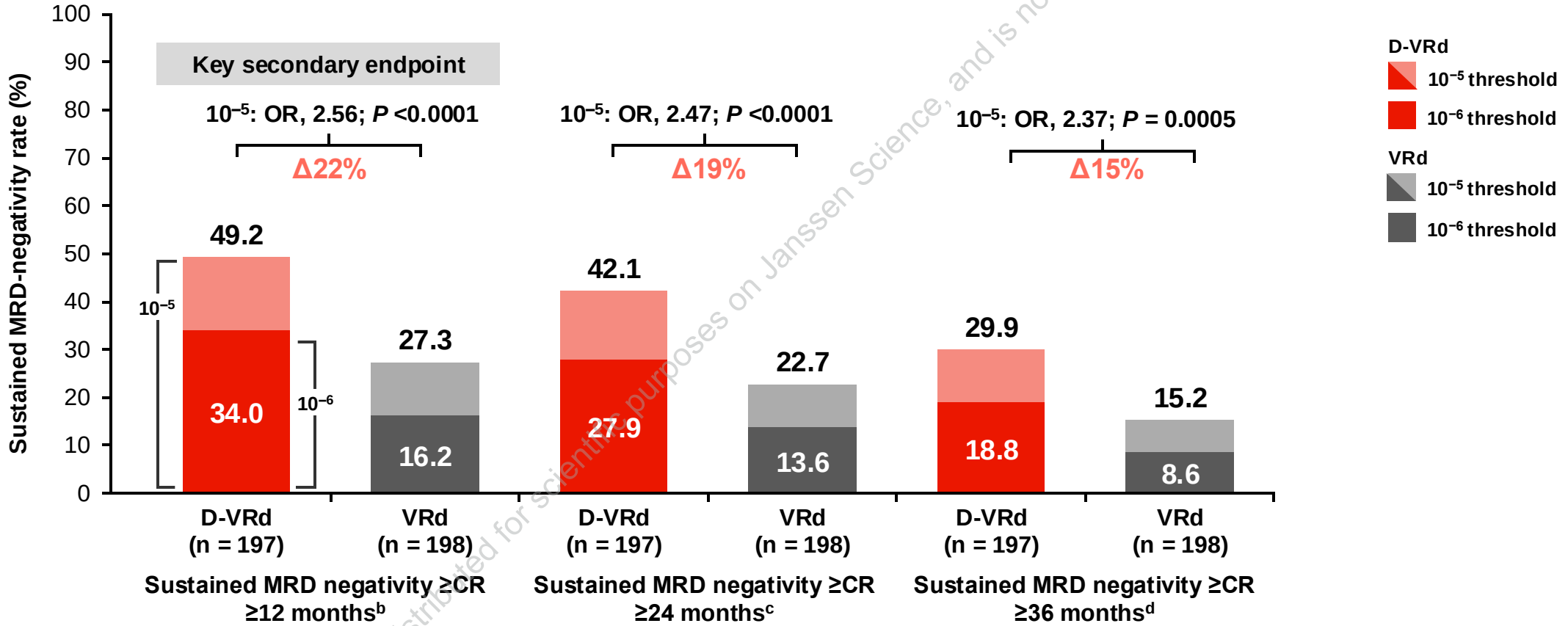
CEPHEUS: Sustained MRD-negativity ≥CR (10^{-5} and 10^{-6}) Rates[a]



Daratumumab almost doubled 12-, 24-, & 36-month sustained MRD-negativity ≥CR rates

[a]At any time on study. [b]Proportion of patients who achieved CR or better response and achieved MRD-negative status at 2 bone marrow assessments that are 12 months apart with an allotted window of ±1 month, without any MRD-positive status in between. [c]Achieving MRD-negative status at 2 bone marrow assessments that are 24 months apart with an allotted window of ±3 months, without any MRD-positive status in between. [d]Achieving MRD-negative status at 2 bone marrow assessments that are 36 months apart, with an allotted window of ±3 months, without any MRD-positive status in between.

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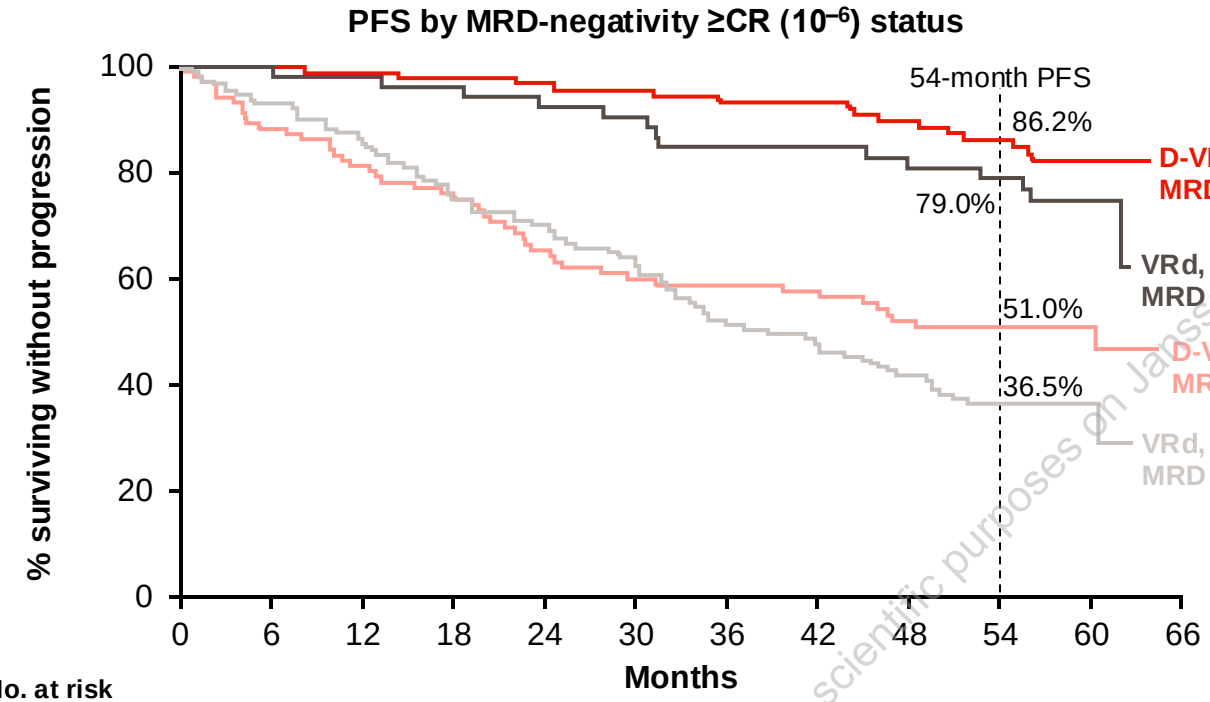
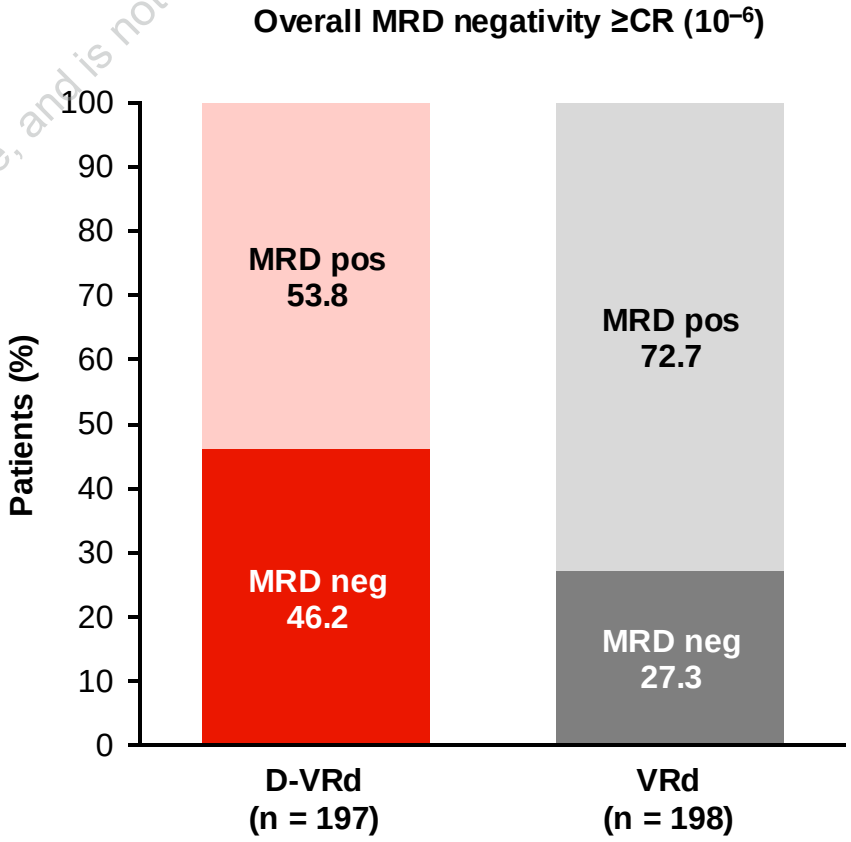
CEPHEUS: PFS by MRD-negativity ≥CR (10^{-6}) Status



No. at risk												
VRd MRD negative	54	54	52	51	49	48	45	44	41	40	15	0
VRd MRD positive	144	120	105	92	82	75	60	54	47	41	6	0
D-VRd MRD negative	91	91	90	89	88	86	83	80	76	72	20	0
D-VRd MRD positive	106	89	80	71	61	54	53	52	46	43	13	0



Daratumumab provides PFS benefit regardless of MRD-negativity ≥CR status

MRD positive consists of intent-to-treat patients who were not tested and assumed positive, or tested and found positive or indeterminate, or tested and found negative but with no CR.

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CEPHEUS: Conclusions

- CEPHEUS is the fifth phase 3 study in NDMM showing the addition of DARA to SoC regimens improves depth and duration of response, leading to improved PFS
- The addition of DARA to VRd led to higher and deeper rates of overall and sustained MRD negativity ≥CR versus VRd alone
  - DARA improved and deepened MRD responses over time, leading to significantly improved PFS
  - PFS improvement with D-VRd versus VRd was seen in MRD-negative and MRD-positive patients
- Among patients who achieved MRD negativity ≥CR (10^{-6}) with D-VRd, >85% were alive and progression free at 54 months

These data further support daratumumab in combination with VRd as a standard of care for patients with NDMM who are transplant-ineligible or for whom transplant is deferred

SoC, standard-of-care.

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CEPHEUS: Acknowledgments

- Patients who participated in this study and their families/caregivers
- Staff members at the study sites
- Data and safety monitoring committee
- IRC committee members

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