Daratumumab SC + Bortezomib/Lenalidomide/Dexamethasone in Patients With Transplant-ineligible or Transplant-deferred Newly Diagnosed Multiple Myeloma: Results of the Phase 3 CEPHEUS Study

Saad Z Usmani[1], Thierry Facon[2], Vania Hungria[3], Nizar J Bahlis[4], Christopher P Venner[5,6], Marc Braunstein[7], Ludek Pour[8], Josep Marti[9], Supratik Basu[10], Yael C Cohen[11,12], Morio Matsumoto[13], Kenshi Suzuki[14], Cyrille Hulin[15], Sebastian Grosicki[16], Wojciech Legiec[17], Meral Beksac[18], Angelo Maiolino[19], Weiping Liu[20], Jianping Wang[21], Maria Krevvata[21], Lorena Lopez-Masi[22], Jodi Carey[21], Melissa Rowe[23], Robin Carson[21], Sonja Zweegman[24]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]University of Lille, CHU de Lille, Service des Maladies du Sang, Lille, France; [3]Clínica Médica São Germano, São Paulo, Brazil; [4]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada; [5]Department of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [6]BC Cancer – Vancouver Centre, University of British Columbia, Vancouver, BC, Canada; [7]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [8]University Hospital Brno, Brno, Czech Republic; [9]Hospital Universitario Mútua de Terrassa, Terrassa, Spain; [10]Royal Wolverhampton NHS Trust and University of Wolverhampton, CRN West Midlands, NIHR, Wolverhampton, UK; [11]Department of Hematology, Tel-Aviv Sourasky (Ichilov) Medical Center, Tel Aviv, Israel; [12]Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [13]Department of Hematology, National Hospital Organization Shibukawa Medical Center, Gunma, Japan; [14]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [15]Department of Hematology, Hôpital Haut Lévêque, University Hospital, Pessac, France; [16]Department of Hematology and Cancer Prevention, School of Public Health, Medical University of Silesian, Katowice, Poland; [17]Department of Hematology and Bone Marrow Transplantation, St. John of Dukla Oncology Center of Lublin Land, Lublin, Poland; [18]Istinye University, Ankara Liv Hospital, Ankara, Turkey; [19]Instituto Americas de Ensino, Pesquisa e Inovação, Rio de Janeiro, Brazil; [20]Janssen Research & Development, Shanghai, China; [21]Janssen Research & Development, LLC, Spring House, PA, USA; [22]Janssen Research & Development, LLC, Raritan, NJ, USA; [23]Janssen Research & Development, LLC, High Wycombe, UK; [24]Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

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CEPHEUS: Introduction

- In NDMM, achievement of MRD negativity is associated with superior PFS and OS[1,2]
- Daratumumab in frontline quadruplet and triplet standard-of-care regimens improves survival outcomes
  - The phase 3 PERSEUS study (D-VRd with D-R maintenance) demonstrated that daratumumab significantly improved PFS in TE patients with NDMM[3]
  - The phase 3 MAIA study (D-Rd) set a new benchmark, with median OS of 7.5 years in TIE patients with NDMM[4]
- Triplet therapy (D-Rd, VRd) is the current standard of care for TIE patients with NDMM

We report results for the first time from the phase 3 CEPHEUS study evaluating D-VRd versus VRd in patients with NDMM who are TIE or for whom transplant was not planned as initial therapy (transplant deferred)

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; TE, transplant eligible; D-Rd, daratumumab plus lenalidomide/dexamethasone; TIE, transplant ineligible; VRd, bortezomib/lenalidomide/dexamethasone.

1. Munshi NC, et al. *Blood Adv*. 2020;4(23):5988-5999. 2. Perrot A, et al. *Blood*. 2018;132(23):2456-2464. 3. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313. 4. Facon T, et al. Presented at: European Hematology Association (EHA) Hybrid Congress; June 13-16, 2024; Madrid, Spain.

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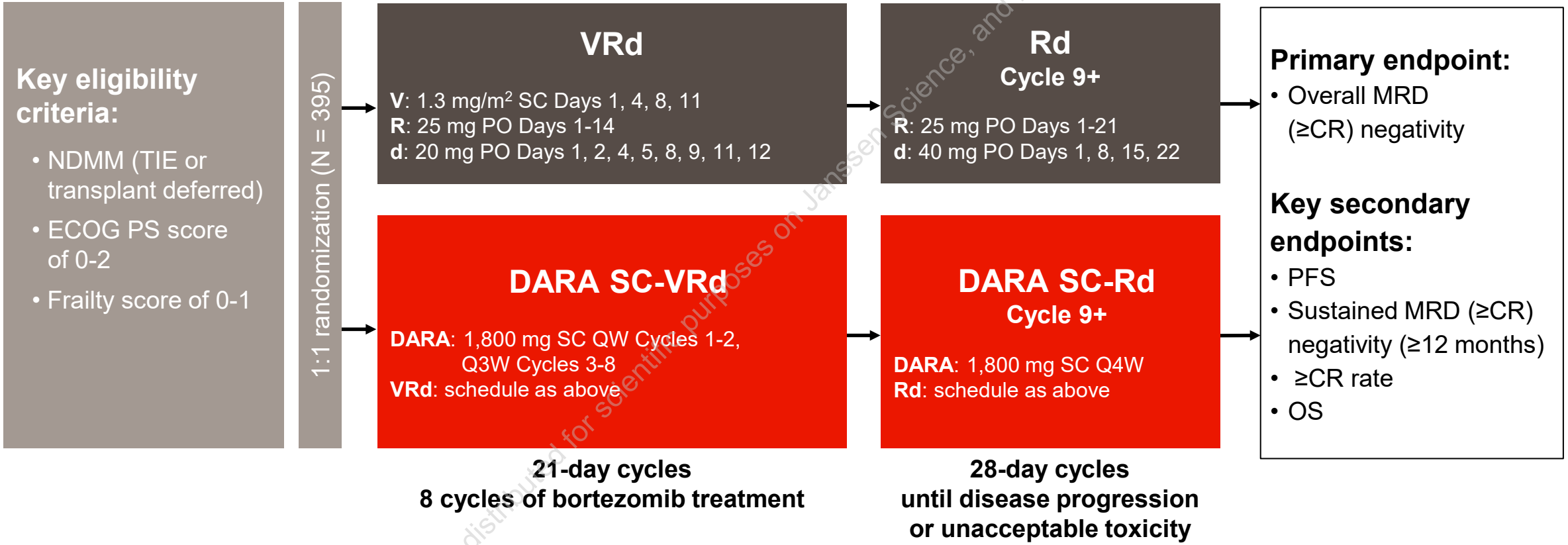
CEPHEUS: Phase 3 Study of DARA SC-VRd Versus VRd in TIE or Transplant-deferred Patients With NDMM



DARA SC, daratumumab and recombinant human hyaluronidase for subcutaneous injection; ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; R, lenalidomide; PO, oral; d, dexamethasone; DARA, daratumumab; QW, weekly; Q3W, every 3 weeks; Q4W, every 4 weeks; CR, complete response.
ClinicalTrials.gov Identifier: NCT03652064. Accessed August 26, 2024.

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CEPHEUS: Baseline Demographic and Clinical Characteristics (ITT Population)

	D-VRd (n = 197)	VRd (n = 198)
Age		
Median (range), years	70.0 (42-79)	70.0 (31-80)
Category, n (%)		
<65 years	36 (18.3)	35 (17.7)
65 to <70 years	52 (26.4)	53 (26.8)
≥70 years	109 (55.3)	110 (55.6)
Male, n (%)	87 (44.2)	111 (56.1)
ECOG PS score, n (%)[a]		
0	71 (36.0)	84 (42.4)
1	103 (52.3)	100 (50.5)
2	23 (11.7)	14 (7.1)
Frailty score, n (%)[b]		
0 (fit)	124 (62.9)	132 (66.7)
1 (intermediate fitness)	73 (37.1)	66 (33.3)
Transplant deferred, n (%)	53 (26.9)	53 (26.8)
Transplant ineligible, n (%)	144 (73.1)	145 (73.2)

	D-VRd (n = 197)	VRd (n = 198)
Type of myeloma by immunofixation or serum FLC assay, n (%)		
IgG	130 (66.0)	114 (57.6)
IgA	38 (19.3)	52 (26.3)
IgD	2 (1.0)	3 (1.5)
Light chain	22 (11.2)	25 (12.6)
Biclonal	5 (2.5)	3 (1.5)
Unknown	0	1 (0.5)
Extramedullary plasmacytomas, n (%)	11 (5.6)	13 (6.6)
ISS disease stage, n (%)[c]		
I	68 (34.5)	68 (34.3)
II	73 (37.1)	75 (37.9)
III	56 (28.4)	55 (27.8)
Cytogenetic risk profile, n (%)[d]		
Standard risk	149 (75.6)	149 (75.3)
High risk	25 (12.7)	27 (13.6)
Indeterminate[e]	23 (11.7)	22 (11.1)

Treatment arms were well balanced

ITT, intent-to-treat; FLC, free light chain; ISS, International Staging System.
[a]ECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. [b]Total additive frailty is scored on a scale of 0 to 5 based on age, comorbidities, and cognitive and physical conditions, with 0 indicating fit, 1 indicating intermediate fitness, and ≥2 indicating frail, per the Myeloma Geriatric Assessment score (http://www.myelomafrailtyscorecalculator.net/). [c]Based on the combination of serum β2-microglobulin and albumin levels. Higher stages indicate more advanced disease. [d]Based on fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16). [e]Indeterminate includes patients with missing or unevaluable samples.

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CEPHEUS: Patient Disposition (ITT Population)

Median follow-up: 58.7 months

	D-VRd	VRd
Randomized patients (ITT)	197	198
Number of patients treated	197	195
Median treatment duration, months	56.3	34.3
Patients who discontinued study treatment,[a] n (%)	95 (48.2)	128 (65.6)
Reason for treatment discontinuation,[a] n (%)		
Progressive disease	27 (13.7)	51 (26.2)
Adverse events	16 (8.1)	32 (16.4)
Death[b]	34 (17.3)	24 (12.3)
Death due to COVID-19	12 (6.1)	6 (3.1)
Other[c]	18 (9.1)	21 (10.8)

TEAE, treatment-emergent adverse event.
[a]Percentages are based on the number of patients treated. [b]Treatment discontinuations due to death are different than grade 5 TEAEs. [c]"Other" included patients who refused further treatment, physician decision, and patients who received concurrent treatment for multiple myeloma prior to disease progression.

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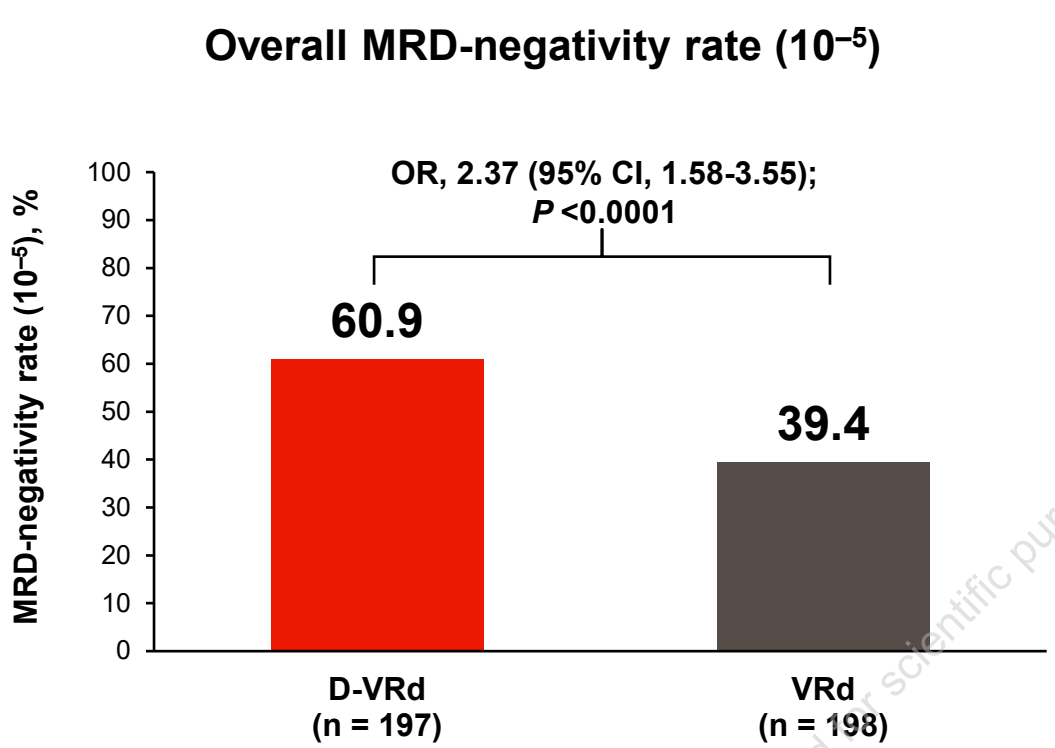
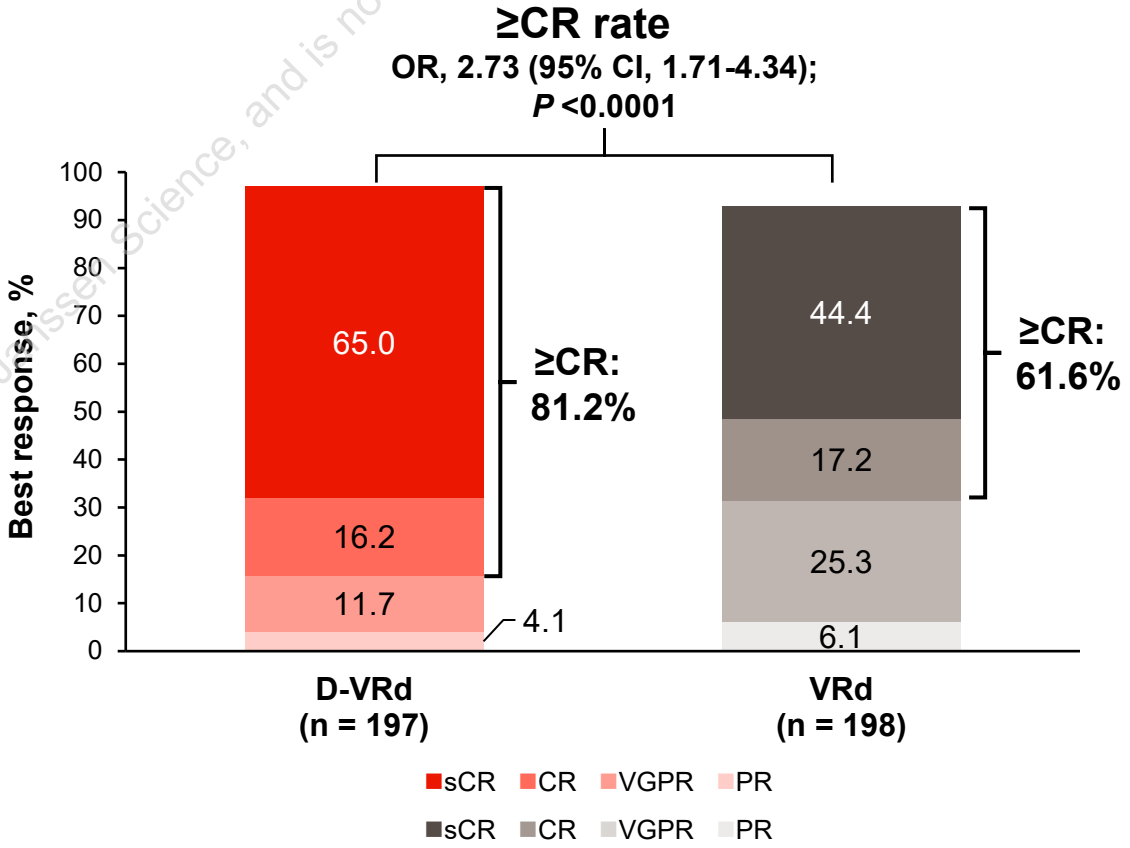
CEPHEUS: Primary Endpoint of Overall MRD-negativity Rate[a] (10^{-5}; ITT Population)





Daratumumab significantly increased overall MRD-negativity rate and overall ≥CR rate by approximately 20%

OR, odds ratio; CI, confidence interval; sCR, stringent complete response; VGPR, very good partial response; PR, partial response.
[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5}) and ≥CR.

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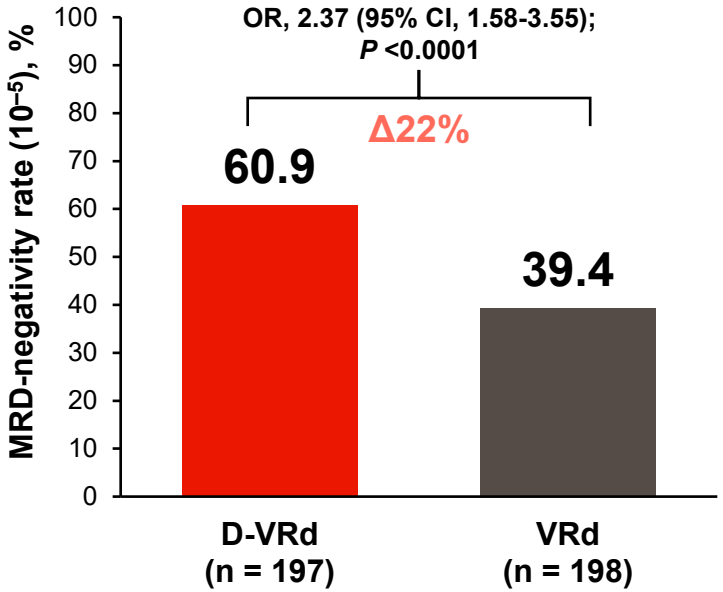
CEPHEUS: Overall and Sustained MRD-negativity Rates[a] (ITT Population)

Primary endpoint

Overall MRD-negativity rate (10^{-5})

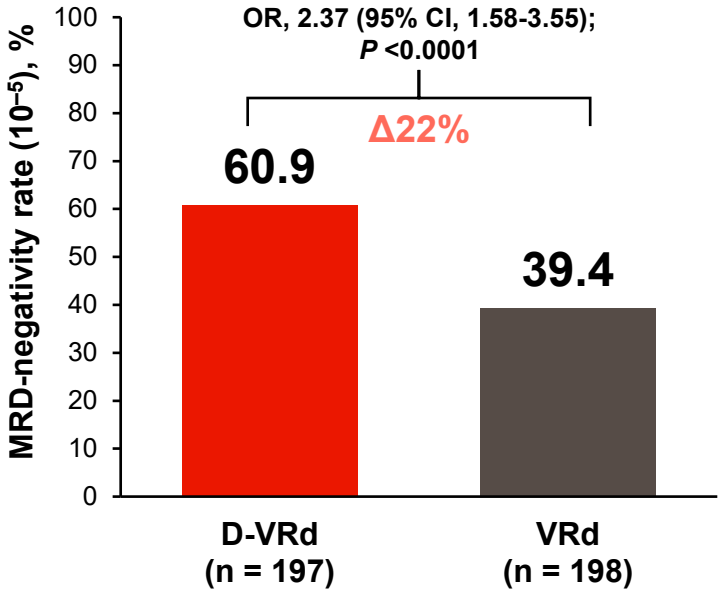


[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5}) and ≥CR.

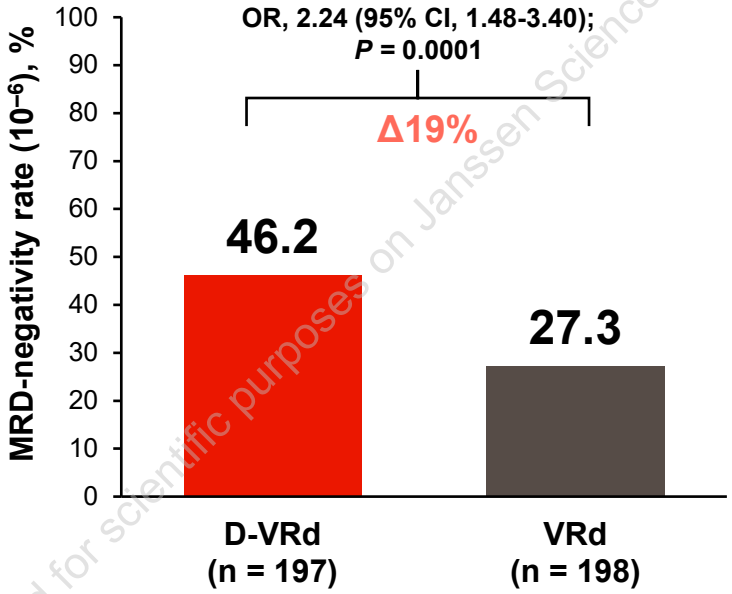
CEPHEUS: Overall and Sustained MRD-negativity Rates[a] (ITT Population)

Primary endpoint

Overall MRD-negativity rate (10^{-5})



Overall MRD-negativity rate (10^{-6})



[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5}) and ≥CR.

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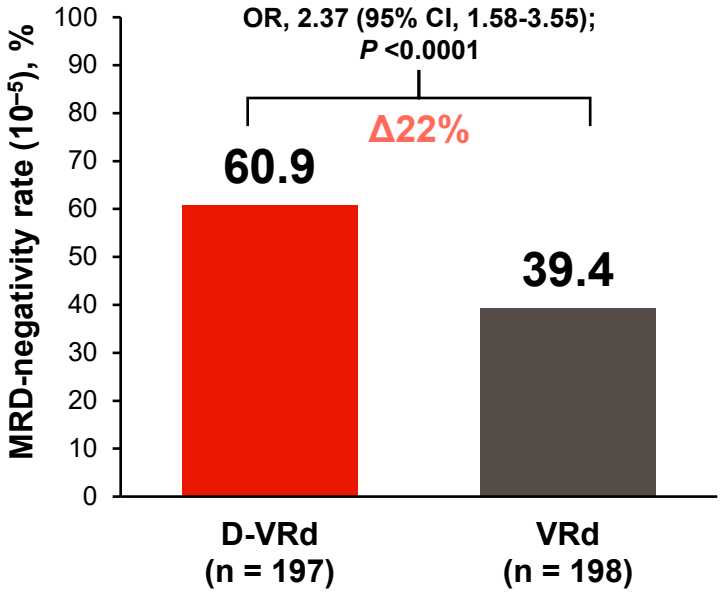
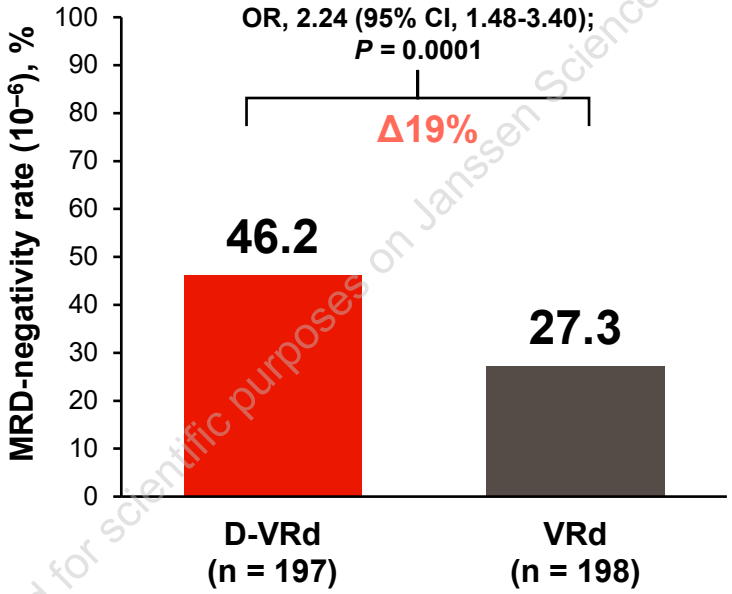
CEPHEUS: Overall and Sustained MRD-negativity Rates[a] (ITT Population)

Primary endpoint

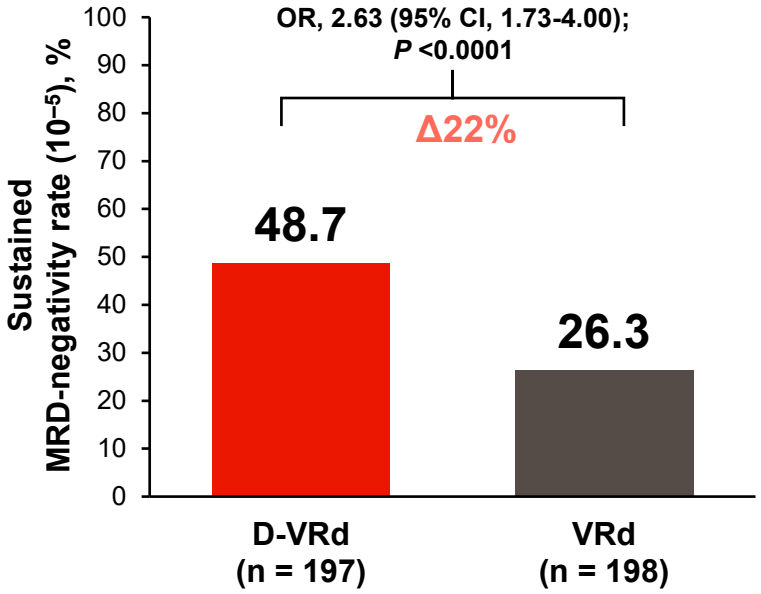
Overall MRD-negativity rate (10^{-5})



Overall MRD-negativity rate (10^{-6})



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



Daratumumab led to deeper MRD responses at 10^{-6} and a higher sustained MRD-negativity rate

[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5}) and ≥CR.

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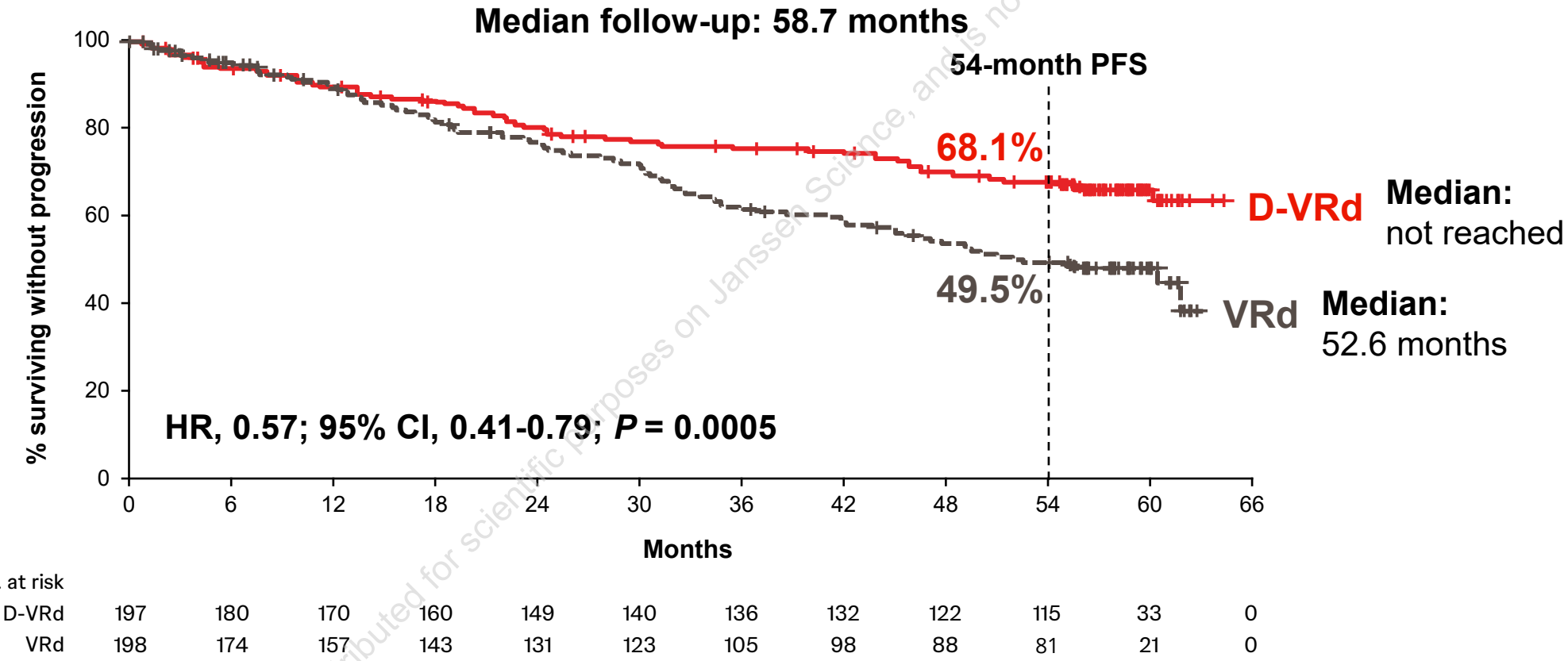
CEPHEUS: PFS (ITT Population)



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

HR, hazard ratio.

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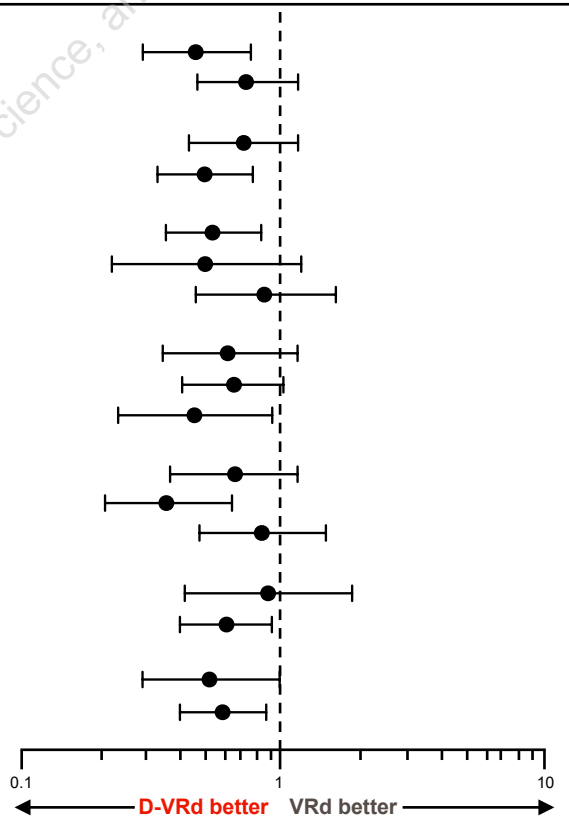
CEPHEUS: PFS in Prespecified Subgroups (ITT Population)

Subgroup	Disease progression or death, n/N		Median PFS, months		HR (95% CI)
	D-VRd	VRd	D-VRd	VRd	
Sex					
Male	24/87	53/111	NE	49.2	0.46 (0.29-0.75)
Female	39/110	38/87	NE	NE	0.73 (0.47-1.15)
Age					
<70 years	30/88	38/88	NE	NE	0.72 (0.44-1.16)
≥70 years	33/109	53/110	NE	49.4	0.50 (0.33-0.78)
Region					
Europe	37/120	54/116	NE	51.1	0.54 (0.36-0.82)
North America	10/37	13/31	NE	50.2	0.51 (0.22-1.17)
Other	16/40	24/51	NE	NE	0.87 (0.46-1.64)
Weight					
≤65 kg	17/58	24/63	NE	NE	0.62 (0.34-1.16)
>65-85 kg	34/101	40/88	NE	51.1	0.65 (0.41-1.02)
>85 kg	12/38	27/47	NE	41.9	0.46 (0.23-0.91)
ISS disease stage					
I	21/68	28/68	NE	60.6	0.66 (0.37-1.16)
II	18/73	37/75	NE	45.6	0.36 (0.21-0.64)
III	24/56	26/55	NE	49.2	0.84 (0.48-1.46)
Cytogenetic risk					
High risk	13/25	17/27	39.8	31.7	0.88 (0.42-1.84)
Standard risk	43/149	60/149	NE	60.6	0.61 (0.41-0.91)
ECOG PS score					
0	16/71	30/84	NE	NE	0.53 (0.29-0.97)
≥1	47/126	61/114	NE	43.8	0.59 (0.40-0.86)



Daratumumab benefit was generally consistent across prespecified subgroups

NE, not estimable.

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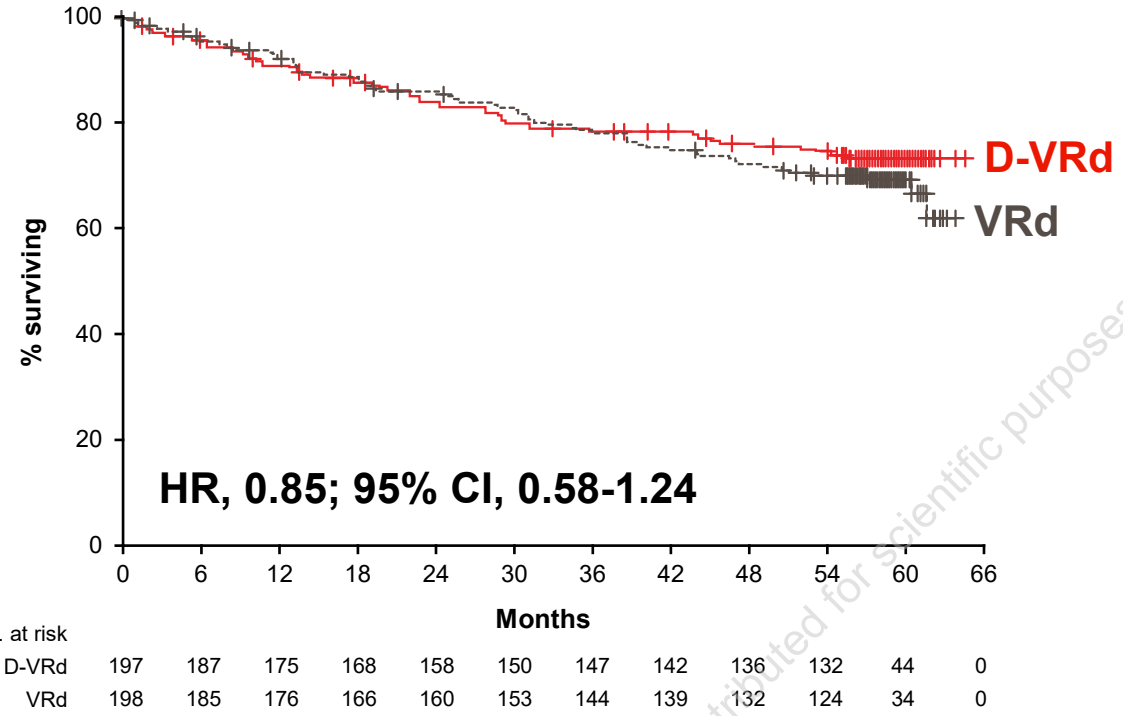
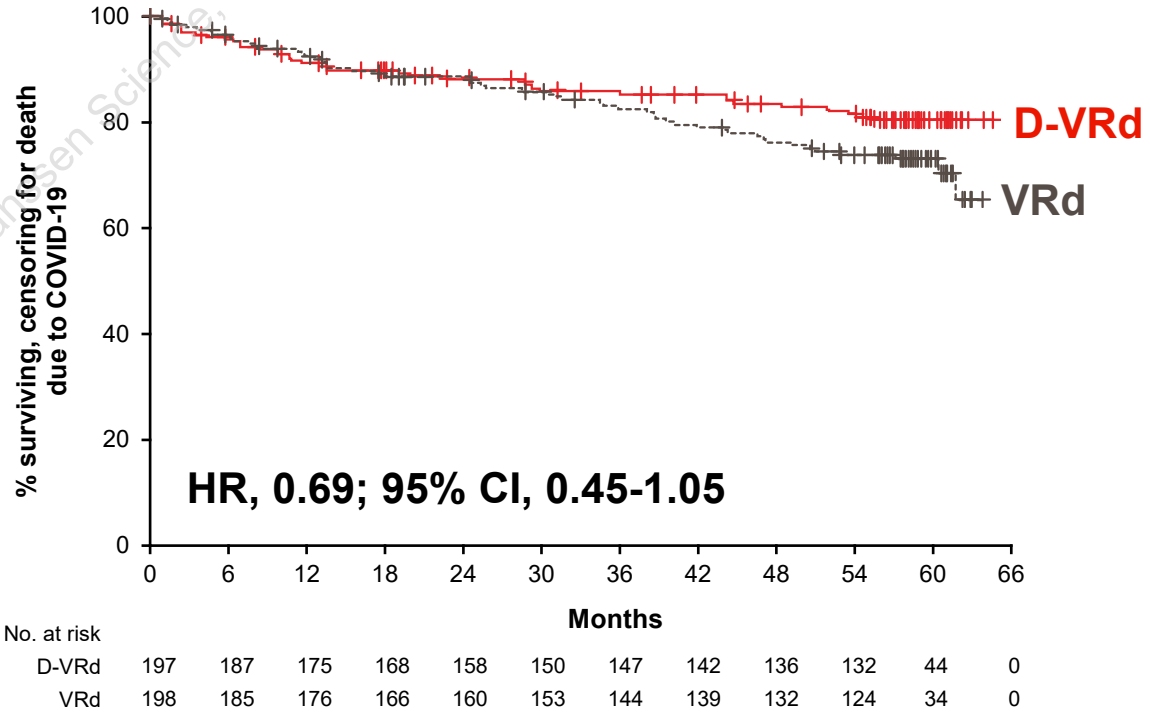
CEPHEUS: OS

OS (ITT population)



No. at risk												
D-VRd	197	187	175	168	158	150	147	142	136	132	44	0
VRd	198	185	176	166	160	153	144	139	132	124	34	0

OS
Censoring for death due to COVID-19



No. at risk												
D-VRd	197	187	175	168	158	150	147	142	136	132	44	0
VRd	198	185	176	166	160	153	144	139	132	124	34	0

OS trended favorably for the daratumumab arm and further improved when censoring for death due to COVID-19

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CEPHEUS: Safety[a]

	D-VRd (n = 197)	VRd (n = 195)
Median (range) treatment duration, months	56.3 (0.1-64.6)	34.3 (0.5-63.8)
Any grade 3 or 4 TEAE, n (%)	182 (92.4)	167 (85.6)
TEAE leading to discontinuation of all study drugs, n (%)	15 (7.6)	31 (15.9)
Grade 5 non–COVID-19 TEAE,[b] n (%)	21 (10.7)	15 (7.7)
Grade 5 COVID-19 TEAE,[b,c] n (%)	12 (6.1)	6 (3.1)
Exposure-adjusted grade 5 TEAE rate, patient-months	0.39/100	0.31/100

- **Comparable rate of grade 5 TEAEs, adjusting for a ~2-year difference in treatment duration**
- **The impact of COVID-19 on grade 5 TEAEs was greatest at the peak of the global pandemic**

[a]The safety population included patients who received ≥1 dose of study treatment. [b]Deaths on or within 30 days of treatment. [c]Includes COVID-19 and COVID-19 pneumonia.

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CEPHEUS: Safety[a]

TEAE, n (%)	D-VRd (n = 197)		VRd (n = 195)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
HEMATOLOGIC				
Blood and lymphatic system disorders	163 (82.7)	126 (64.0)	126 (64.6)	98 (50.3)
Neutropenia	110 (55.8)	87 (44.2)	76 (39.0)	58 (29.7)
Thrombocytopenia	92 (46.7)	56 (28.4)	66 (33.8)	39 (20.0)
Anemia	73 (37.1)	26 (13.2)	62 (31.8)	23 (11.8)
NONHEMATOLOGIC				
Gastrointestinal disorder	157 (79.7)	41 (20.8)	159 (81.5)	40 (20.5)
Diarrhea	112 (56.9)	24 (12.2)	115 (59.0)	18 (9.2)
Constipation	75 (38.1)	4 (2.0)	82 (42.1)	5 (2.6)
General disorders and administration-site conditions	159 (80.7)	40 (20.3)	147 (75.4)	28 (14.4)
Peripheral edema	83 (42.1)	4 (2.0)	76 (39.0)	1 (0.5)
Fatigue	63 (32.0)	18 (9.1)	60 (30.8)	16 (8.2)
Psychiatric disorders	91 (46.2)	10 (5.1)	96 (49.2)	10 (5.1)
Insomnia	63 (32.0)	4 (2.0)	63 (32.3)	2 (1.0)
Infections	181 (91.9)	79 (40.1)	167 (85.6)	62 (31.8)
Upper respiratory tract infection	78 (39.6)	1 (0.5)	64 (32.8)	1 (0.5)
COVID-19	75 (38.1)	22 (11.2)	48 (24.6)	9 (4.6)
Second primary malignancies	15 (7.6)	–	18 (9.2)	–

	Any grade	Grade 2	Grade 3 or 4	Any grade	Grade 2	Grade 3 or 4
Peripheral sensory neuropathy	110 (55.8)	60 (30.5)	16 (8.1)	119 (61.0)	70 (35.9)	16 (8.2)

Safety data was consistent with the established safety profile of each individual drug

[a]The safety population included patients who received ≥1 dose of study treatment.

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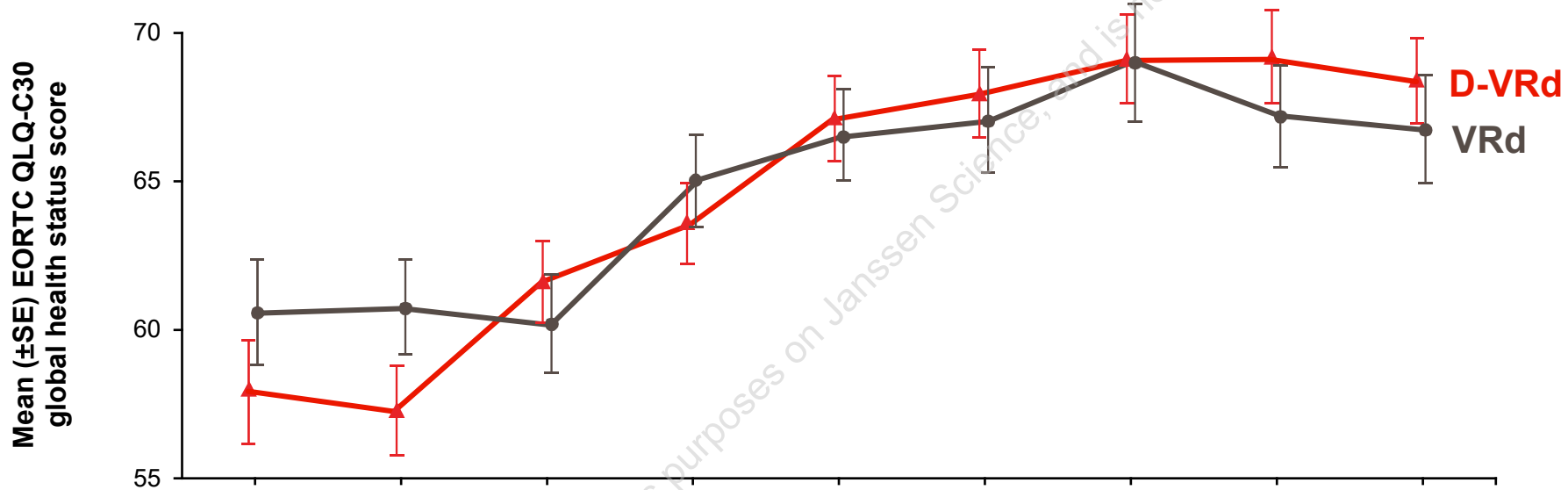
CEPHEUS: Quality of Life by EORTC QLQ-C30



No. of patients									
D-VRd	174	185	173	166	154	144	141	140	137
VRd	174	179	175	158	141	128	119	116	106

Quality of life improved in both arms over time with no detriment due to daratumumab

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.
Quality of life was assessed using the EORTC QLQ-C30.

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CEPHEUS: Conclusions

- CEPHEUS is the first phase 3 daratumumab trial with a primary endpoint of MRD negativity
- Adding daratumumab to VRd significantly improved depth and duration of response
  - Primary endpoint of overall MRD negativity (10^{-5}): 60.9% vs 39.4%
  - Overall MRD-negativity (10^{-6}): 46.2% vs 27.3%
  - Sustained MRD-negativity (10^{-5}): 48.7% vs 26.3%
- Risk of disease progression or death was 43% lower for D-VRd, HR: 0.57
- OS trended favorably for D-VRd, improving further when censored for COVID-19 deaths, HR: 0.69
- D-VRd quadruplet has the potential to improve clinical outcomes for TIE or transplant-deferred patients with NDMM who can tolerate bortezomib

CEPHEUS complements MAIA (D-Rd), supporting a daratumumab-based quadruplet or triplet standard-of-care option across TIE patients and those deferring transplant

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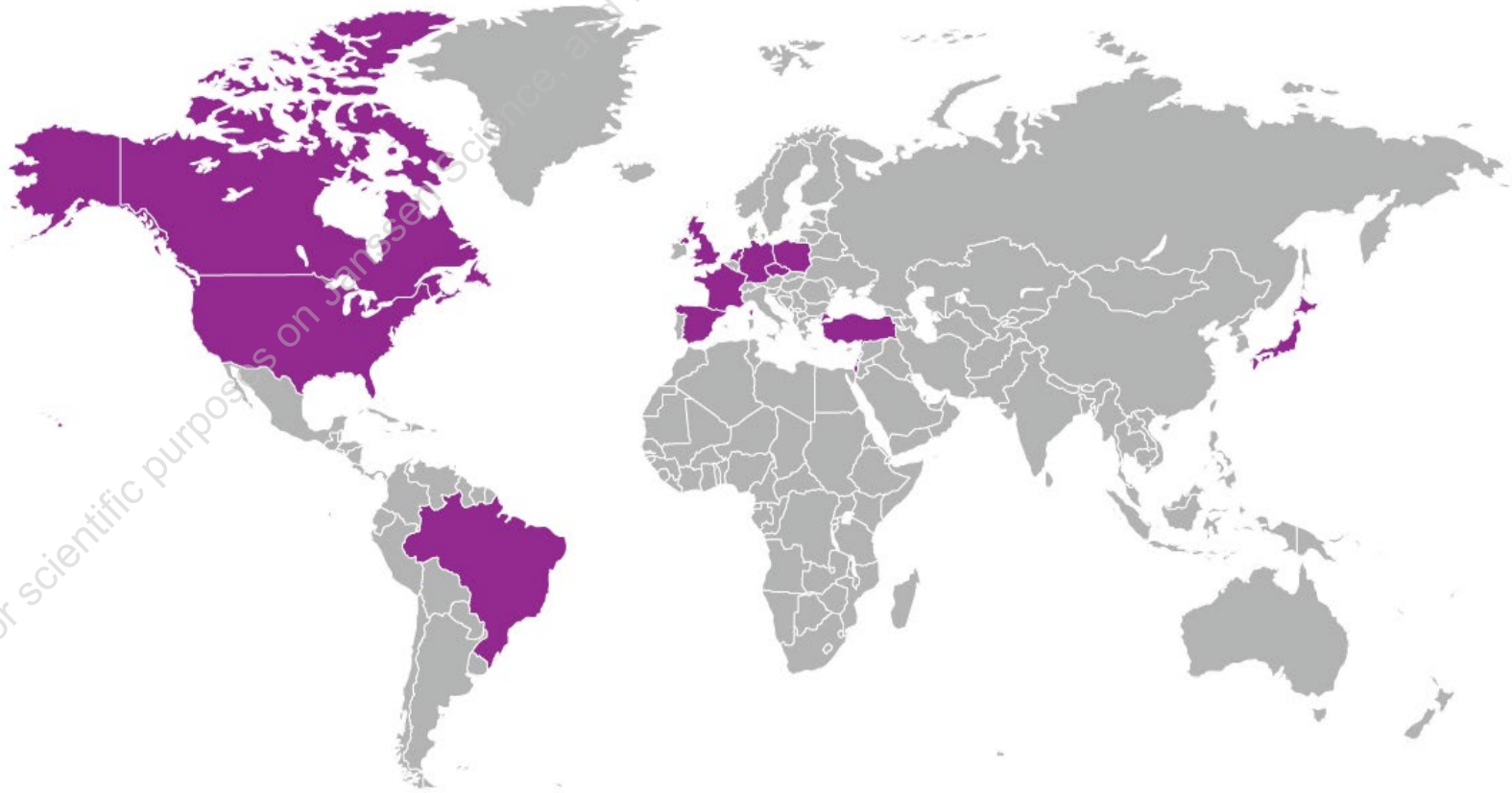
CEPHEUS: Acknowledgments

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



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https://www.congresshub.com/Oncology/IMS2024/Daratumumab/Usmani-Dara

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