Daratumumab Plus Bortezomib, Lenalidomide, and Dexamethasone (DVRd) in Patients With Newly Diagnosed Multiple Myeloma (NDMM): Subgroup Analysis of Transplant-Ineligible (TIE) Patients in the Phase 3 CEPHEUS Study

Thierry Facon[1], Sonja Zweegman[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], Yaël C Cohen[11,12], Morio Matsumoto[13], Kenshi Suzuki[14], Cyrille Hulin[15], Sebastian Grosicki[16], Meral Beksac[17], Angelo Maiolino[18], Jianping Wang[19], Melissa Rowe[20], Robin L Carson[19], Saad Z Usmani[21]

[1]University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France; [2]Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [3]Clínica Médica São Germano, São Paulo, Brazil; [4]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada; [5]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]Tel Aviv Sourasky (Ichilov) Medical Center, Tel Aviv, Israel; [12]Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [13]National Hospital Organization Shibukawa Medical Center, Gunma, Japan; [14]Japanese Red Cross Medical Center, Tokyo, Japan; [15]Hôpital Haut Lévêque, University Hospital, Pessac, France; [16]School of Public Health, Medical University of Silesia, Katowice, Poland; [17]Istinye University, Ankara Liv Hospital, Ankara, Turkey; [18]Instituto Americas de Ensino, Pesquisa e Inovação, Rio de Janeiro, Brazil; [19]Johnson & Johnson, Spring House, PA, USA; [20]Johnson & Johnson, High Wycombe, UK; [21]Memorial Sloan Kettering Cancer Center, New York, NY, USA

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CEPHEUS TIE Subgroup: Key Takeaways

- In the CEPHEUS trial, DVRd vs VRd in patients with TIE NDMM led to:
  - Improved depth and duration of response with higher rates of overall MRD (10^{-5}) negativity (60.4% vs 39.3%; OR, 2.37; 95% CI, 1.47–3.80) and higher rates of sustained ≥1-year and ≥2-year MRD negativity
  - Improved PFS (HR, 0.51; 95% CI, 0.35–0.74), with higher proportion of patients alive and progression free at 4.5 years (69% vs 48%)
  - Trends toward improved OS (HR, 0.66), especially when censoring for death due to COVID-19 (HR, 0.55)
  - No additional safety concerns compared with the ITT population in this older, frailer TIE subgroup

Results of this post hoc CEPHEUS TIE subgroup analysis reinforce DVRd as standard of care for the treatment of TIE NDMM

DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OR, odds ratio; OS, overall survival; PFS, progression-free survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

Introduction

- Daratumumab-containing triplet and quadruplet regimens (eg, DRd, DVRd) have demonstrated improved survival benefit in patients with NDMM[1-4]
  - DVRd is a recommended option for the treatment of TE[5-7] and TIE NDMM[6,7]
  - The phase 3 MAIA trial showed significant and clinically meaningful improvement in PFS and OS with DRd vs Rd for patients with TIE NDMM,[3] a population for which DRd remains a recommended treatment[5-7]
- In the phase 3 CEPHEUS trial, DVRd improved overall MRD-negativity rates and PFS vs VRd in patients with NDMM who were TIE or who deferred transplant[4]
  - A subgroup analysis of CEPHEUS also demonstrated a consistent benefit of DVRd vs VRd regardless of frailty status[8]
- Transplant deferral is not a common clinical pathway for NDMM in many regions, and the majority of patients enrolled in CEPHEUS were TIE (approximately 75%)

This post hoc CEPHEUS subgroup analysis evaluates the efficacy and safety outcomes of DVRd in TIE NDMM

MAIA: NCT02252172; CEPHEUS: NCT03652064. DRd, daratumumab, lenalidomide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; TE, transplant eligible; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Facon T. et al. *N Engl J Med* 2019;380:2104-15. 2. Sonneveld P, et al. *N Engl J Med* 2024;390:301-13. 3. Facon T, et al. *Leukemia* 2025;39:942-50. 4. Usmani, SZ, et al. *Nat Med* 2025;31:1195-1202.

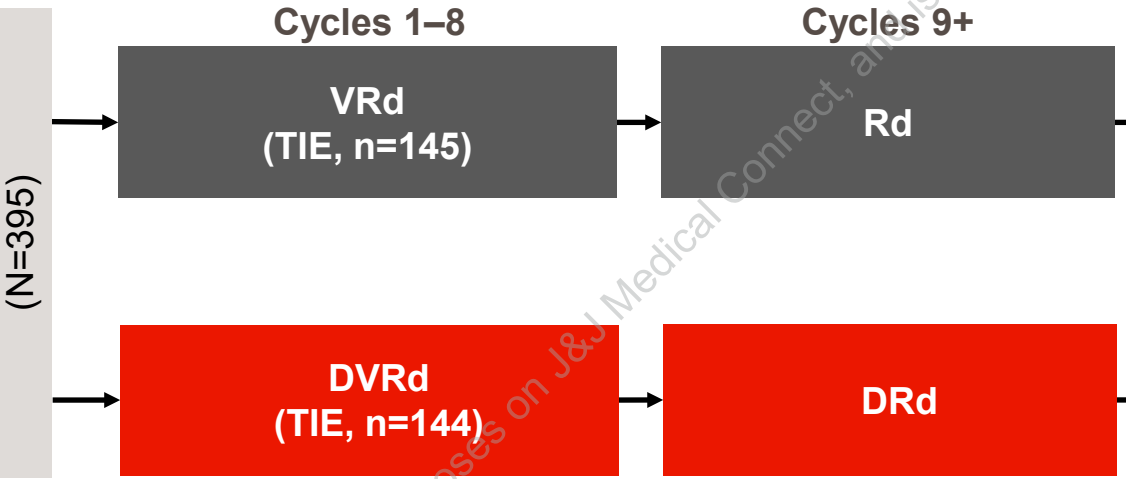
6. Rajkumar SV. *Am J Hematol* 2024;99:1802-24. 7. mSMART. Treatment for Multiple Myeloma v22. 8. Zweegman S, et al. Presented at EMN; April 10, 2025; Athens, Greece.

CEPHEUS: Study Design

Key eligibility criteria:

- NDMM (TIE or transplant deferred)
- ECOG PS score 0-2
- IMWG frailty score 0-1

1:1 randomization (N=395)



Primary endpoint:

- Overall MRD (≥CR) negativity[a]

Key secondary endpoints:

- PFS
- Sustained (≥12 months) MRD negativity ≥CR
- ≥CR rate
- OS

This post hoc subgroup analysis includes only patients with TIE NDMM (~75% of the ITT population)

[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. CR, complete response; DRd, daratumumab, lenalidomide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone. ClinicalTrials.gov Identifier: NCT03652064. Accessed April 7, 2025. Usmani, SZ, et al. *Nat Med*. 2025;31:1195-1202.

CEPHEUS TIE Subgroup: Baseline Demographic and Clinical Characteristics

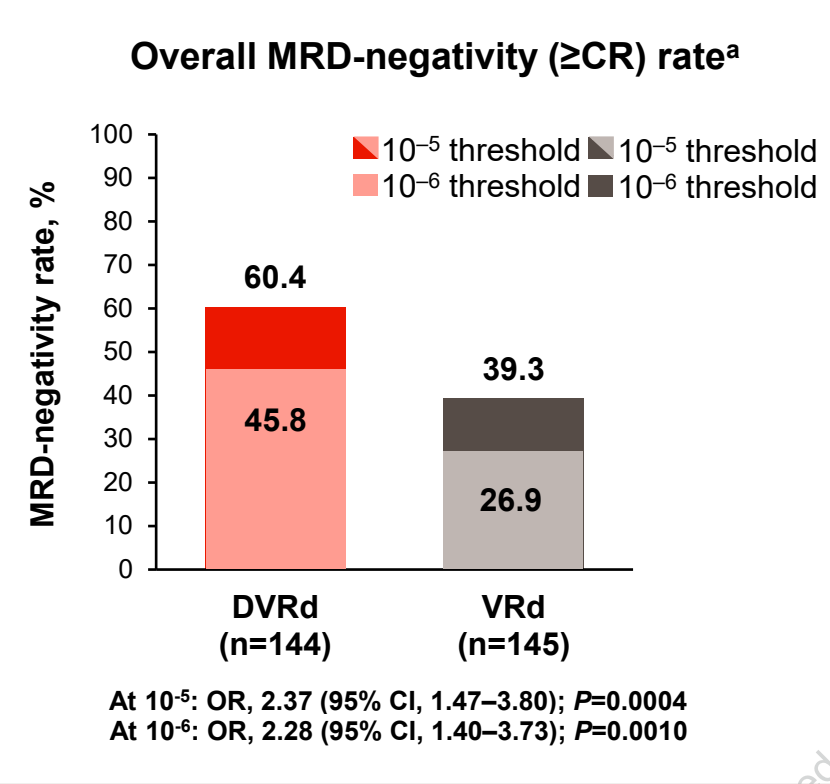
Characteristic	DVRd (n=144)	VRd (n=145)
Age		
Median (range), years	72.0 (58–79)	72.0 (51–80)
Age <70 years, n (%)	35 (24.3)	35 (24.1)
Age 70 to <75 years, n (%)	68 (47.2)	65 (44.8)
Age ≥75 years, n (%)	41 (28.5)	45 (31.0)
Male, n (%)	65 (45.1)	82 (56.6)
ECOG PS score, n (%)[a]		
0	52 (36.1)	57 (39.3)
1	75 (52.1)	78 (53.8)
2	17 (11.8)	10 (6.9)
IMWG frailty score, n (%)[b]		
0 (fit)	82 (56.9)	88 (60.7)
1 (intermediate fitness)	62 (43.1)	57 (39.3)
IFM frailty score, n (%)		
Nonfrail (0–1)	96 (66.7)	110 (75.9)
Frail (≥2)	48 (33.3)	35 (24.1)

Characteristic	DVRd (n=144)	VRd (n=145)
Type of myeloma by immunofixation or serum FLC assay, n (%)		
IgG	92 (63.9)	78 (53.8)
IgA	26 (18.1)	42 (29.0)
IgD	2 (1.4)	2 (1.4)
Light chain	20 (13.9)	19 (13.1)
Biclonal	4 (2.8)	3 (2.1)
Unknown	0	1 (0.7)
Extramedullary plasmacytomas, n (%)	9 (6.3)	12 (8.3)
ISS staging, n (%)[c]		
I	50 (34.7)	48 (33.1)
II	54 (37.5)	57 (39.3)
III	40 (27.8)	40 (27.6)
Cytogenetic risk, n (%)[d]		
Standard	105 (72.9)	111 (76.6)
High	20 (13.9)	18 (12.4)
Unevaluable or missing	19 (13.2)	16 (11.0)

Baseline characteristics of TIE patients were similar between DVRd and VRd groups

[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 β_2-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). DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FLC, free light chain; IFM, Intergroupe Francophone du Myelome; Ig, immunoglobulin; IMWG, International Myeloma Working group; ISS, International Staging System; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

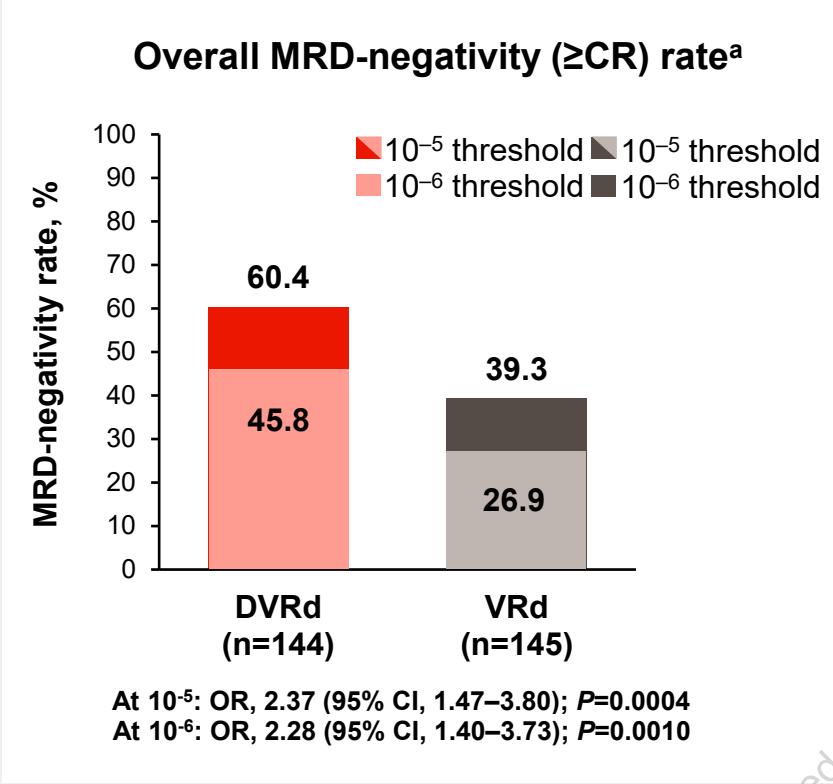
CEPHEUS TIE Subgroup: Overall and Sustained MRD-Negativity ≥CR Rates

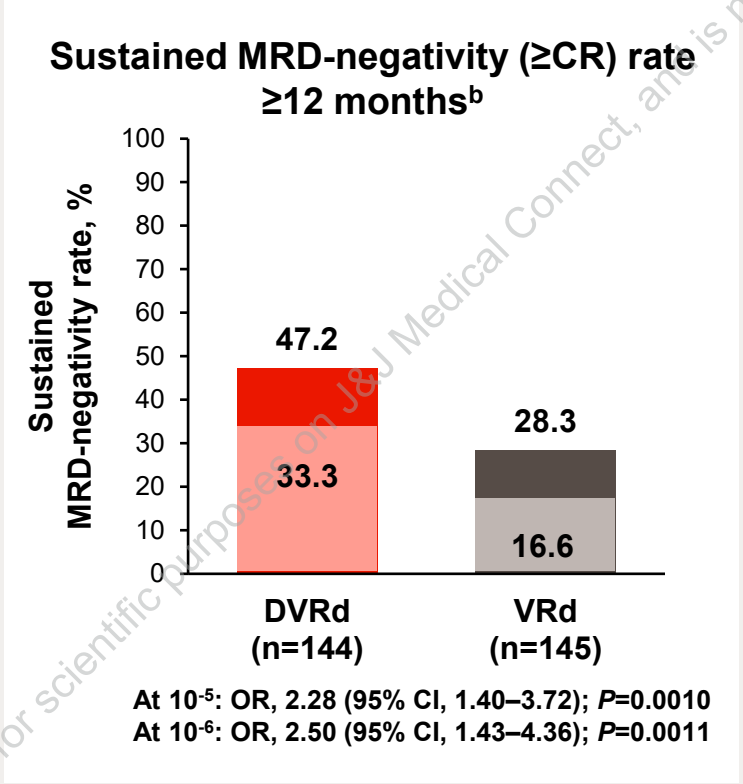


DVRd significantly increased overall MRD-negativity rates at 10^{-5} and 10^{-6} vs VRd

[a]The proportion of patients who achieved MRD negativity and ≥CR. [b]Sustained MRD negativity was defined as 2 consecutive MRD negative reads ≥12 months (±1) or 24 months (±3) apart with no MRD positive result in between.
CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; OR, odds ratio; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS TIE Subgroup: Overall and Sustained MRD-Negativity ≥CR Rates



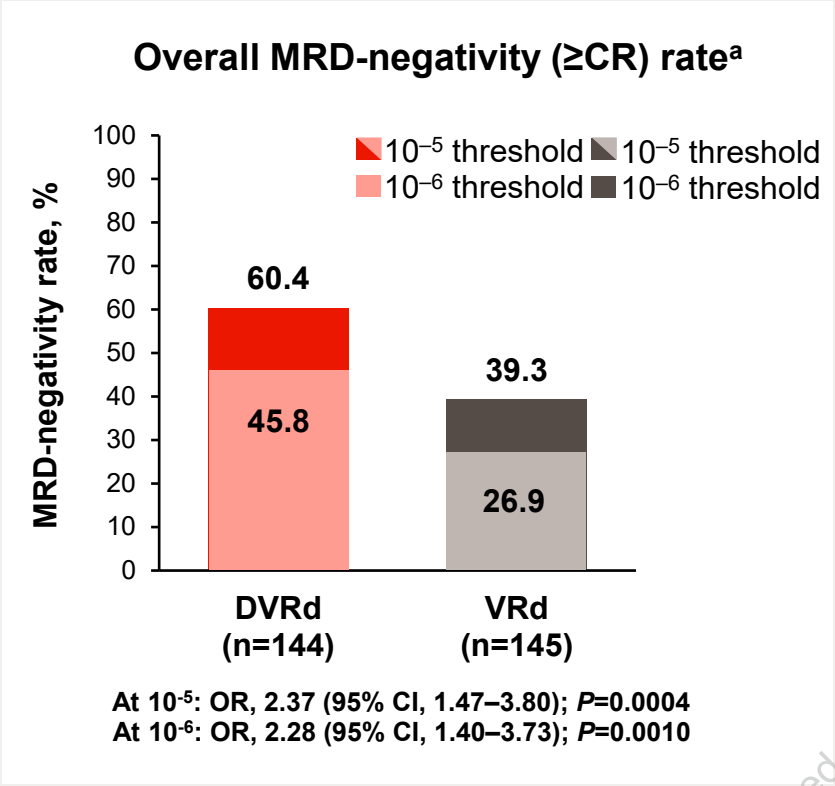


DVRd significantly increased overall MRD-negativity rates at 10^{-5} and 10^{-6} vs VRd

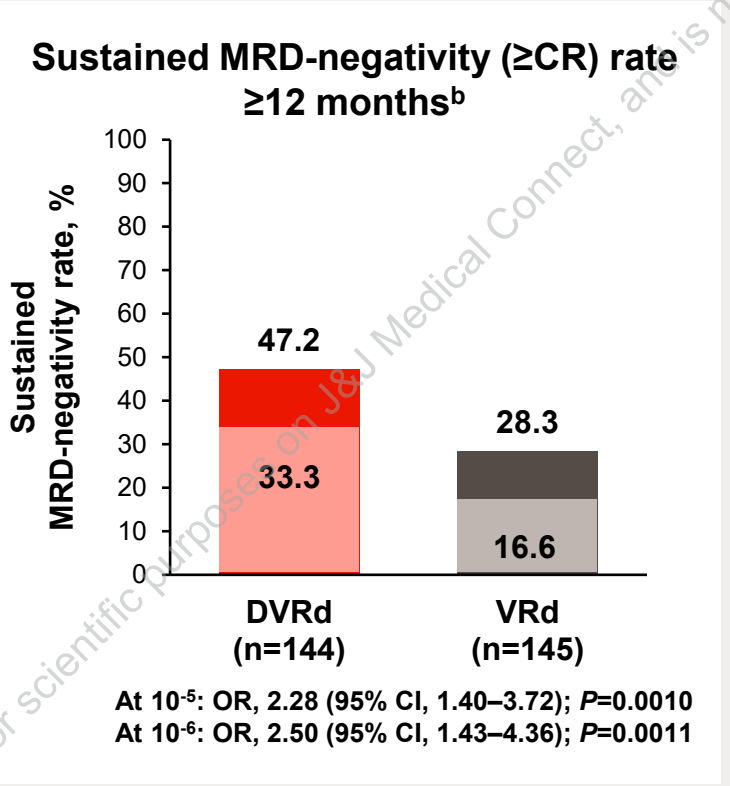
Almost 4 out of 5 patients with MRD-negative ≥CR (10^{-5}) sustained response for ≥1 year

[a]The proportion of patients who achieved MRD negativity and ≥CR. [b]Sustained MRD negativity was defined as 2 consecutive MRD negative reads ≥12 months (±1) or 24 months (±3) apart with no MRD positive result in between.
CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; OR, odds ratio; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

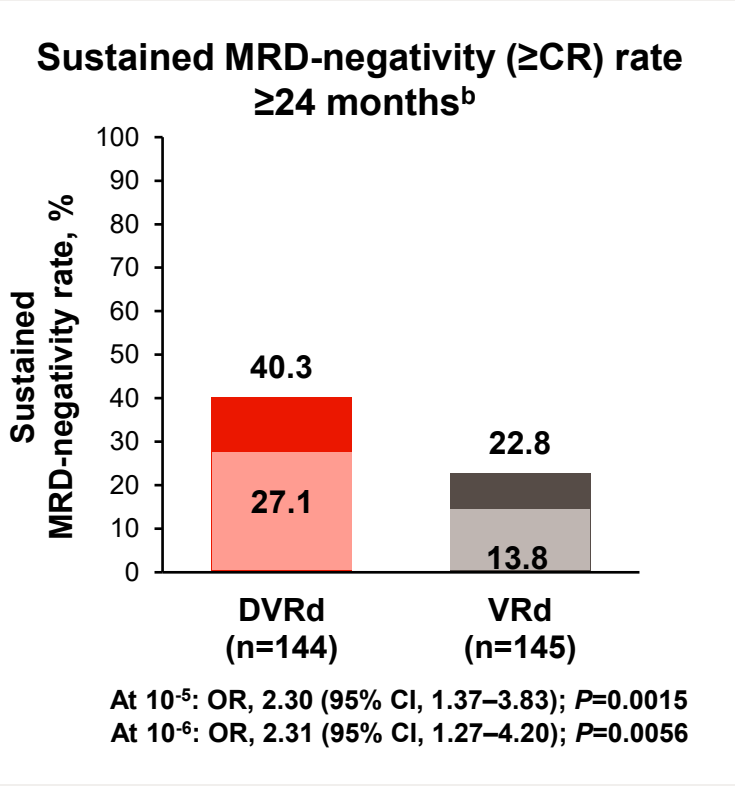
CEPHEUS TIE Subgroup: Overall and Sustained MRD-Negativity ≥CR Rates



At 10^{-5}: OR, 2.37 (95% CI, 1.47–3.80); *P*=0.0004
At 10^{-6}: OR, 2.28 (95% CI, 1.40–3.73); *P*=0.0010



At 10^{-5}: OR, 2.28 (95% CI, 1.40–3.72); *P*=0.0010
At 10^{-6}: OR, 2.50 (95% CI, 1.43–4.36); *P*=0.0011

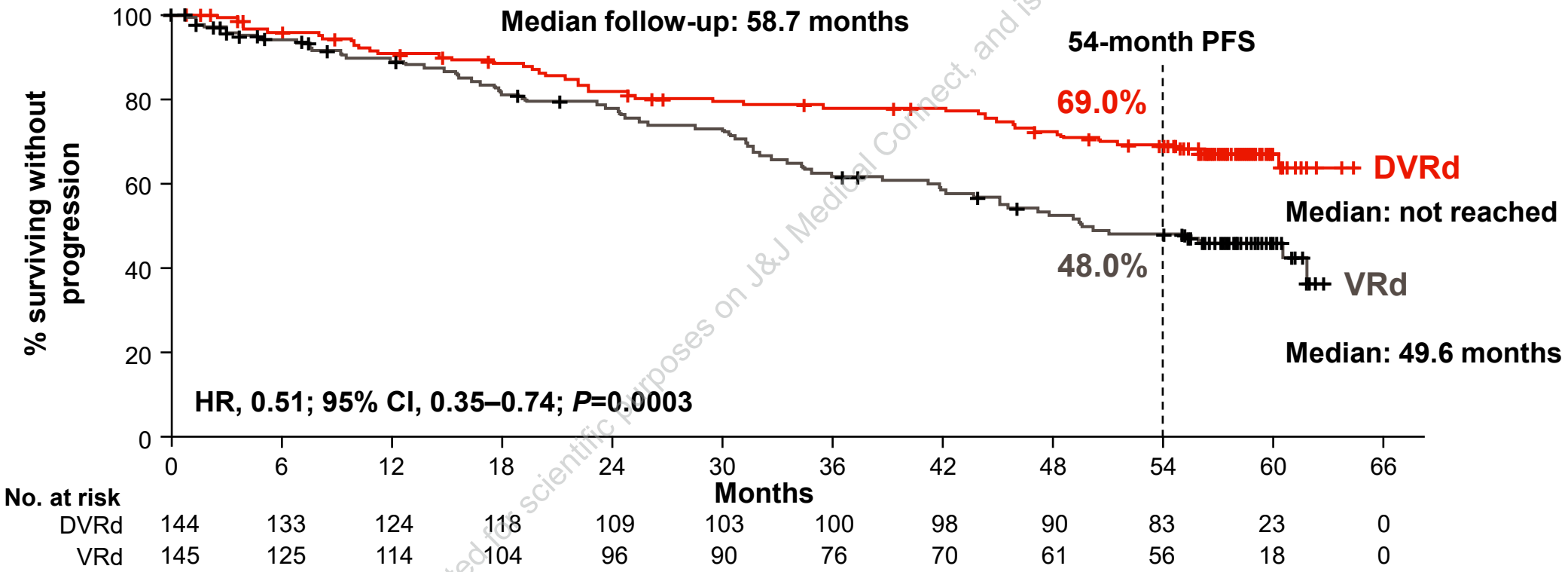


At 10^{-5}: OR, 2.30 (95% CI, 1.37–3.83); *P*=0.0015
At 10^{-6}: OR, 2.31 (95% CI, 1.27–4.20); *P*=0.0056

DVRd significantly increased overall MRD-negativity rates at 10^{-5} and 10^{-6} vs VRd
Almost 4 out of 5 patients with MRD-negative ≥CR (10^{-5}) sustained response for ≥1 year
2 out of 3 patients with MRD-negative ≥CR (10^{-5}) sustained response for ≥2 years

[a]The proportion of patients who achieved MRD negativity and ≥CR. [b]Sustained MRD negativity was defined as 2 consecutive MRD negative reads ≥12 months (±1) or 24 months (±3) apart with no MRD positive result in between.
CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; OR, odds ratio; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS TIE Subgroup: Progression-Free Survival

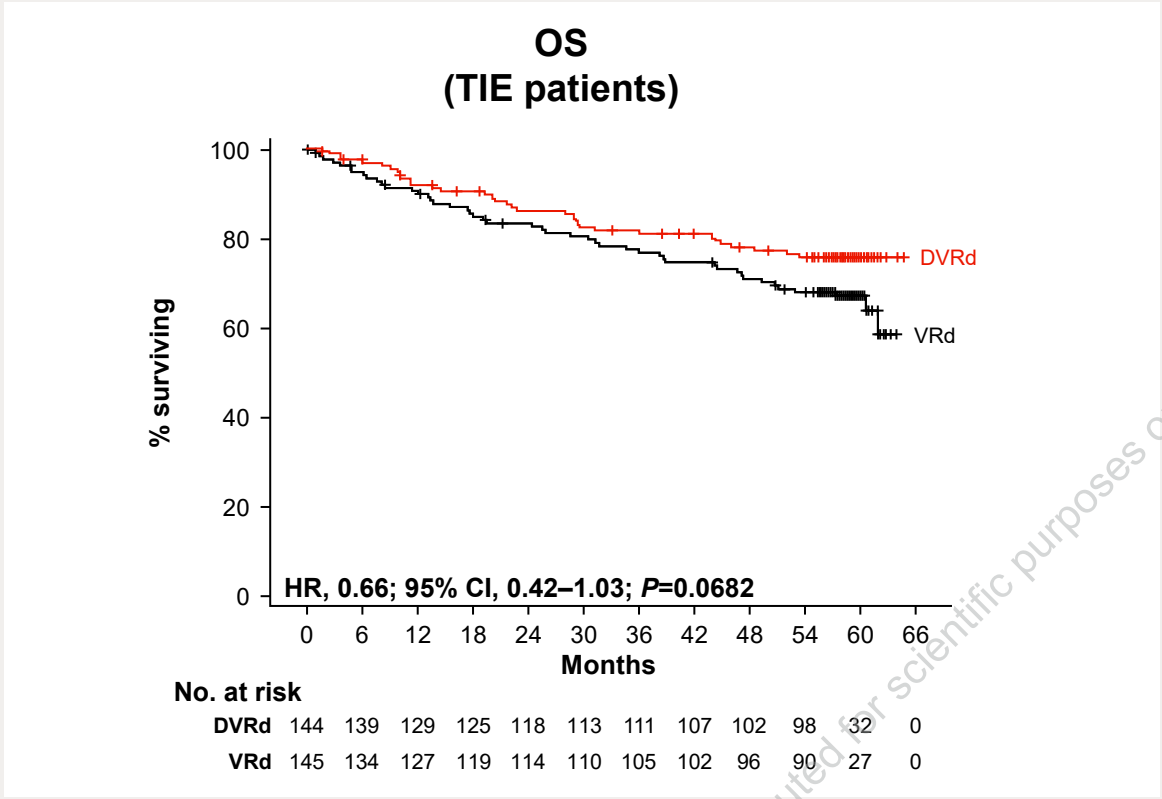


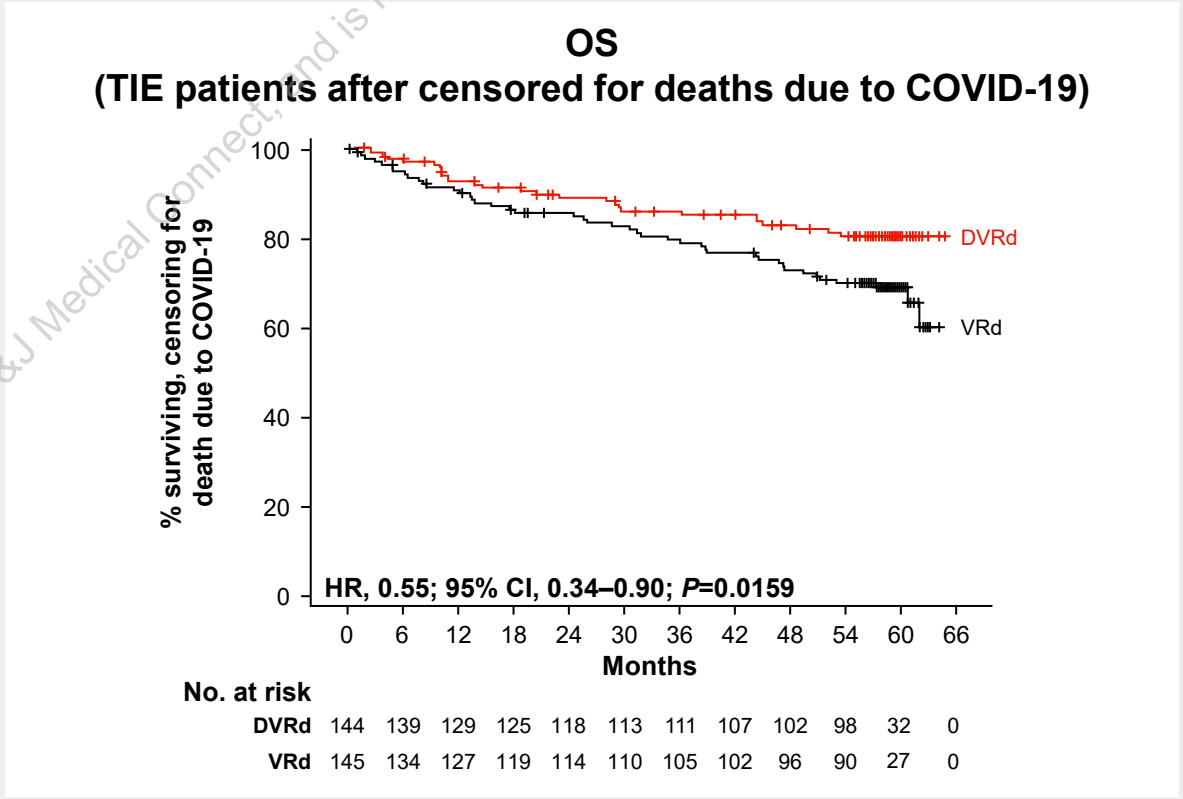
DVRd significantly improved PFS, with a 49% reduction in the risk of disease progression or death – greater than the ITT population (43% reduction in risk with DVRd vs VRd)[1]

DVRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Usmani SZ, et al. *Nat Med* 2025. doi: 10.1038/s41591-024-03485-7.

CEPHEUS TIE Subgroup: Overall Survival



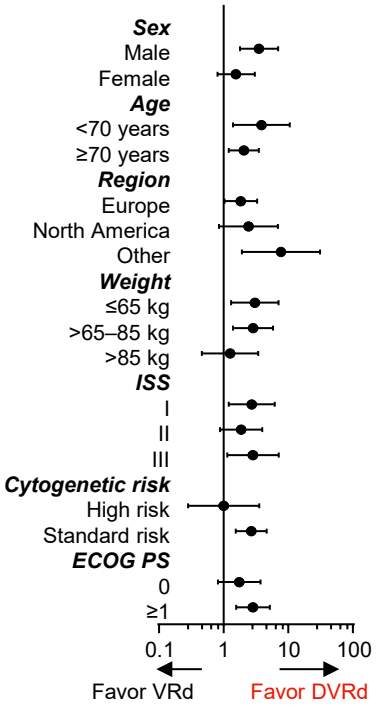


OS trended favorably for the DVRd arm and was significant when censoring for death due to COVID-19; OS HR improved in the TIE subgroup compared with the ITT population

DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; OS, overall survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

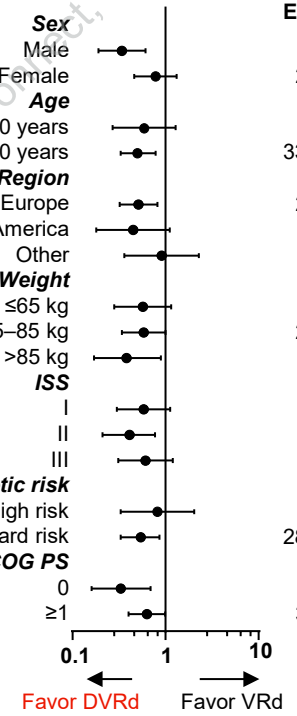
CEPHEUS TIE Subgroup: Overall MRD-Negativity (10^{-5}) With ≥CR and PFS in Prespecified Subgroups

MRD negativity at 10^{-5}



	DVRd n/N (%)	VRd n/N (%)	Odds ratio (95% CI)
Sex			
Male	42/65 (64.6)	28/82 (34.1)	3.52 (1.78–6.97)
Female	45/79 (57.0)	29/63 (46.0)	1.55 (0.80–3.02)
Age			
<70 years	26/35 (74.3)	15/35 (42.9)	3.85 (1.40–10.59)
≥70 years	61/109 (56.0)	42/110 (38.2)	2.06 (1.20–3.53)
Region			
Europe	54/96 (56.3)	37/90 (41.1)	1.84 (1.03–3.30)
North America	20/31 (64.5)	12/28 (42.9)	2.42 (0.85–6.92)
Other	8/27 (29.6)	13/17 (76.5)	7.72 (l.92–31.06)
Weight			
≤65 kg	31/46 (67.4)	19/47 (40.4)	3.05 (1.30–7.11)
>65–85 kg	39/69 (56.5)	20/64 (31.3)	2.86 (1.40–5.82)
>85 kg	17/29 (58.6)	18/34 (52.9)	1.26 (0.46–3.42)
ISS			
I	33/50 (66.0)	20/48 (41.7)	2.72 (1.20–6.17)
II	32/54 (59.3)	25/57 (43.9)	1.86 (0.88–3.96)
III	22/40 (55.0)	12/40 (30.0)	2.85 (1.14–7.15)
Cytogenetic risk			
High risk	10/20 (50.0)	9/18 (50.0)	1.00 (0.28–3.57)
Standard risk	66/105 (62.9)	43/111 (38.7)	2.68 (1.54–4.64)
ECOG PS			
0	30/52 (57.7)	25/57 (43.9)	1.75 (0.82–3.73)
≥1	57/92 (62.0)	32/88 (36.4)	2.85 (1.56–5.22)

PFS



	DVRd Event/N	DVRd mPFS (months)	VRd Event/N	VRd mPFS (months)	Hazard ratio (95% CI)
Sex					
Male	15/65	NE	42/82	47.9	0.34 (0.19–0.61)
Female	29/79	NE	27/63	NE	0.78 (0.46–1.31)
Age					
<70 years	11/35	NE	16/35	NE	0.59 (0.27–1.28)
≥70 years	33/109	NE	53/110	49.4	0.50 (0.33–0.78)
Region					
Europe	29/96	NE	44/90	49.6	0.51 (0.32–0.82)
North America	8/31	NE	12/28	50.2	0.45 (0.18–1.11)
Other	7/17	NE	13/27	NE	0.91 (0.36–2.28)
Weight					
≤65 kg	13/46	NE	19/47	NE	0.57 (0.28–1.15)
>65–85 kg	23/69	NE	31/64	49.2	0.58 (0.34–1.00)
>85 kg	8/29	NE	19/34	42.2	0.38 (0.17–0.89)
ISS					
I	15/50	NE	21/48	60.6	0.58 (0.30–1.12)
II	14/54	NE	28/57	49.4	0.41 (0.21–0.77)
III	15/40	NE	20/40	33.6	0.61 (0.31–1.19)
Cytogenetic risk					
High risk	9/20	NE	11/18	31.7	0.82 (0.33–2.03)
Standard risk	28/105	NE	45/111	60.6	0.54 (0.33–0.86)
ECOG PS					
0	10/52	NE	24/57	60.6	0.33 (0.16–0.69)
≥1	34/92	NE	45/88	47.2	0.63 (0.40–0.99)

Treatment effect was generally consistent across subgroups

CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; mPFS, median progression-free survival; MRD, minimal residual disease; NE, not estimable; PFS, progression-free survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS TIE Subgroup: Safety

Safety overview

Event, n (%)	DVRd (n=144)	VRd (n=142)
Any TEAE	144 (100)	142 (100)
Grade 3 and 4	115 (79.9)	113 (79.6)
Grade 5 non–COVID-19	13 (9.0)	12 (8.5)
Grade 5 COVID-19[a]	6 (4.2)	1 (0.7)
Any serious TEAE	104 (72.2)	99 (69.7)
TEAE leading to discontinuation of all study treatment	11 (7.6)	27 (19.0)
Total deaths during study	33 (22.9)	46 (32.4)
Exposure-adjusted grade 5 TEAE rate, patient-months	0.27/100	0.31/100
Second primary malignancies	14 (9.7)	16 (11.3)

Common (≥5%) grade 3 or 4 TEAEs of interest

Event, n (%)	DVRd (n=144)	VRd (n=142)
Neutropenia	63 (43.8)	45 (31.7)
Thrombocytopenia	44 (30.6)	33 (23.2)
Anemia	18 (12.5)	18 (12.7)
Diarrhea	17 (11.8)	14 (9.9)
Fatigue	13 (9.0)	15 (10.6)
COVID-19[b]	14 (9.7)	5 (3.5)
Pneumonia	20 (13.9)	17 (12.0)
Peripheral sensory neuropathy	Any Grade: 86 (59.7) Grade 3/4: 14 (9.7)	Any Grade: 90 (63.4) Grade 3/4: 12 (8.5)

DVRd showed no additional safety concerns in this older, frailer TIE subgroup compared with the ITT population of CEPHEUS

[a]Deaths on or within 30 days of treatment. [b]Group term. DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ITT, intent to treat; TEAE, treatment-emergent adverse event; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS TIE Subgroup: Conclusions

- The phase 3 CEPHEUS trial previously demonstrated improved efficacy outcomes with DVRd vs VRd in patients with TIE or transplant-deferred NDMM[1]
- In this post hoc analysis of the TIE subgroup, DVRd improved depth and duration of response:
  - Overall MRD negativity: 60.4% vs 39.3% at 10^{-5}; 45.8% vs 26.9% at 10^{-6}
  - 12-month sustained MRD negativity: 47.2% vs 28.3% at 10^{-5}; 33.3% vs 16.6% at 10^{-6}
  - 24-month sustained MRD negativity: 40.3% vs 22.8% at 10^{-5}; 27.1% vs 13.8% at 10^{-6}
- Risk of disease progression or death was 49% lower for DVRd vs VRd; HR, 0.51
- OS favored DVRd (HR, 0.66), especially when censoring for death due to COVID-19 (HR, 0.55)
- No additional safety concerns in this older, frailer TIE subgroup compared with the ITT

Results of this post hoc CEPHEUS TIE subgroup analysis reinforce DVRd as standard of care for the treatment of TIE NDMM

CEPHEUS: NCT03652064. DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Usmani SZ, et al. *Nat Med* 2025. doi: 10.1038/s41591-024-03485-7.

CEPHEUS: Acknowledgments

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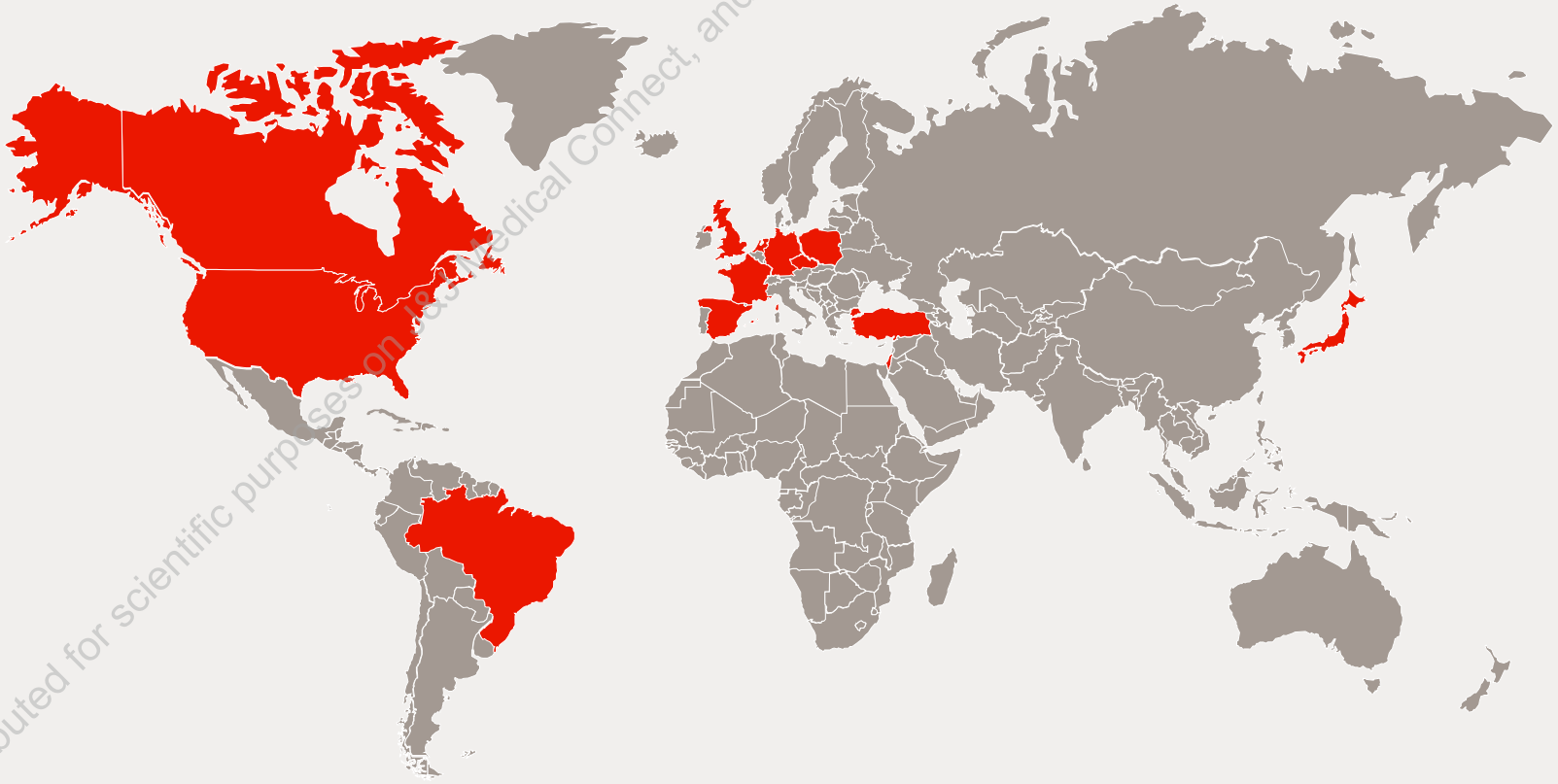

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