Patient-Reported Outcomes and Safety in Patients With NDMM Achieving MRD Negativity and ≥CR in the Phase 3 PERSEUS and CEPHEUS Trials

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Disclosures

- J San Miguel declares participation on advisory boards and consulting services, on behalf of his institution, for:
  - AbbVie, Amgen, BMS, Celgene, GSK, Haemalogix, Johnson & Johnson, Karyopharm, MSD, Novartis, Pfizer, Takeda, Regeneron, Roche, Sanofi, SecuraBio, and Gilead-Kite

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PROs and Safety in Patients With NDMM Achieving MRD Negativity: Key Takeaways

- Up to now, there has been **a lack of evidence** regarding the impact of achieving **MRD negativity** vs remaining MRD positive on **HRQoL** in patients with NDMM

- **DVRd** is a **new standard of care** in the treatment of patients with NDMM, regardless of transplant eligibility, based on **improved survival** underpinned by **superior MRD-negativity rates** vs VRd, demonstrated in both the **PERSEUS and CEPHEUS** phase 3 studies

- Here, we show **for the first time** that achievement of **MRD negativity** was associated with **favorable PROs and exposure-adjusted safety outcomes** vs MRD-positive patients treated with current standard-of-care treatment for NDMM

DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HRQoL, health-related quality of life; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; PRO, patient-reported outcome; VRd, bortezomib, lenalidomide, and dexamethasone.

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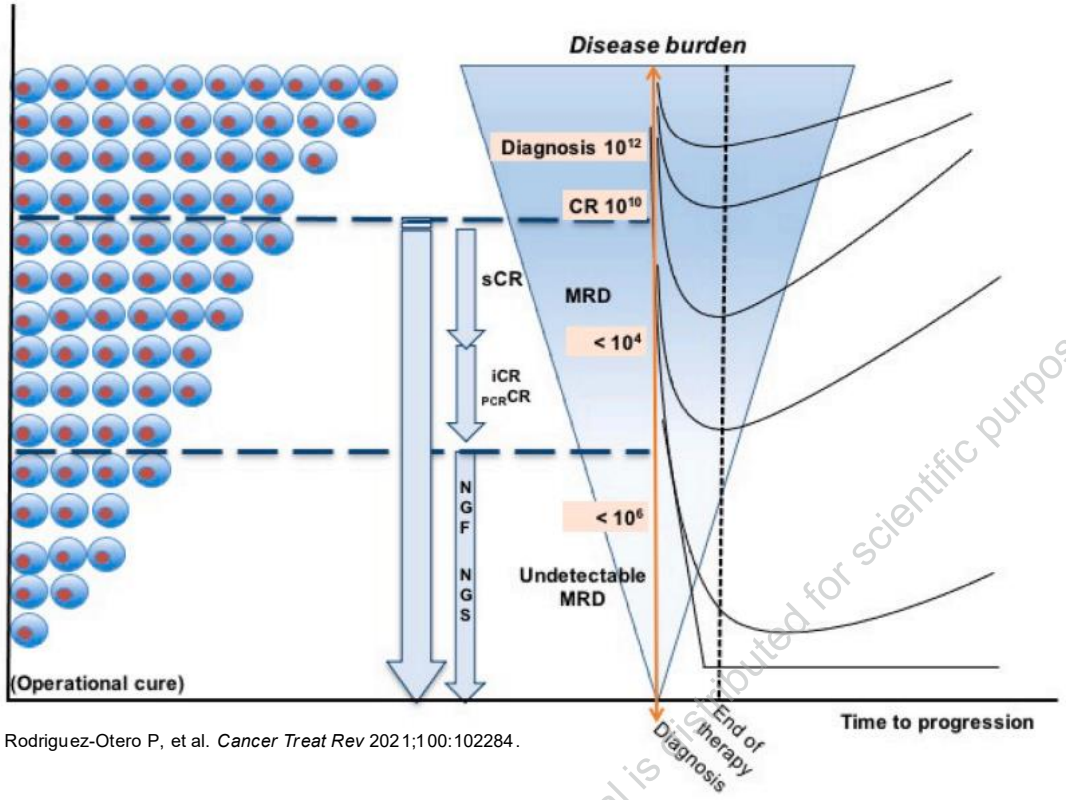
MRD Negativity Is a New Endpoint of Myeloma Therapy[1]

The goal of therapy in cancer is to eradicate all tumor cells



Rodriguez-Otero P, et al. *Cancer Treat Rev* 2021;100:102284.

- There are precise methods used to measure MRD both inside (NGS/NGF) and outside (PET [MRI]) the bone marrow[1,2]
- MRD is a reservoir for clonal evolution and disease recurrence[2]
- MRD is predictive in newly diagnosed and relapsed patients[2]
- Confirmed by different techniques and labs[1]
- Impact on both high- and standard-risk patients[2]

CR, complete response; iCR, immunophenotypic complete response; MRD, minimal residual disease; MRI, magnetic resonance imaging; NGF, next-generation flow; NGS, next-generation sequencing; PCRCR, polymerase chain reaction complete response; PET, positron emission tomography; sCR, stringent complete response.

1. Harousseau J-L, Avet-Loiseau H. *J Clin Oncol* 2017;35(25):2863-5. 2. Rodriguez-Otero P, et al. *Cancer Treat Rev* 2021;100:102284.

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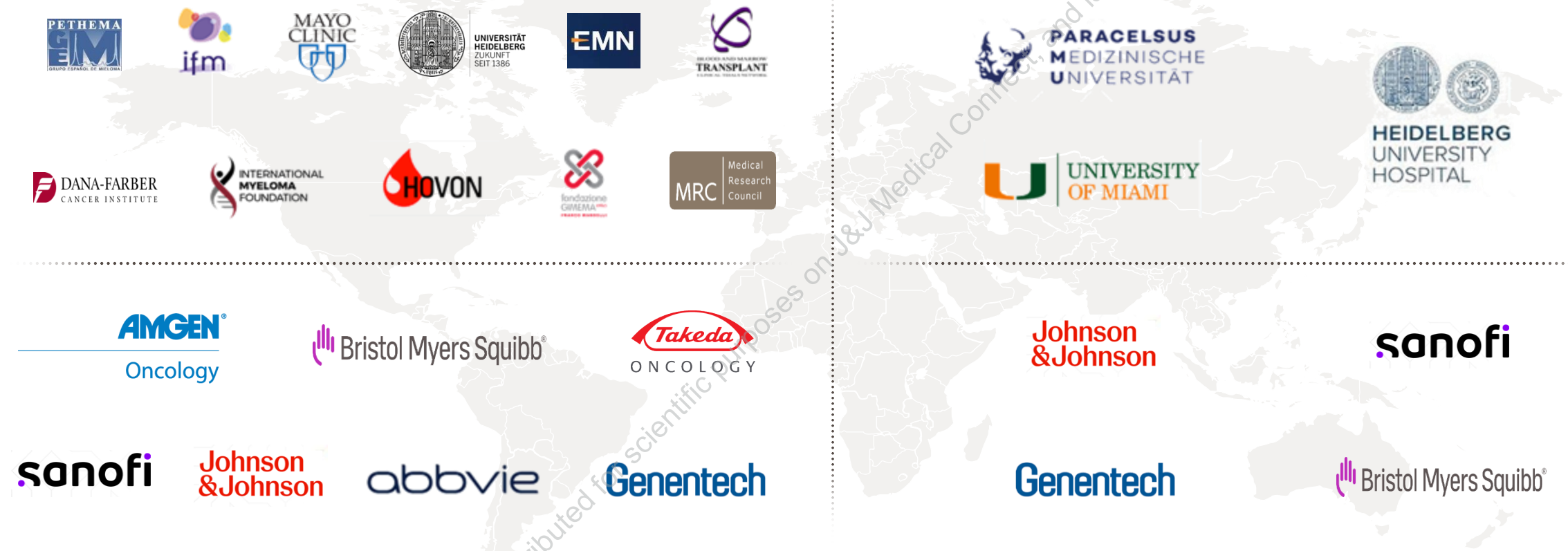
International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i²TEAMM)[1]

Evaluating Minimal Residual Disease as an Intermediate Clinical Endpoint for Multiple Myeloma: The EVIDENCE Meta-Analysis[2]



Long-standing efforts *of the International Myeloma Foundation, Academic Centers, and Industry that* ***worked together searching for MRD as a*** *new endpoint that will represent a sensitive early readout for conditional drug approval,* ***allowing patients timely access to newer treatment options,*** *although trials should be adequately planned to demonstrate a benefit in PFS or OS*

CR, complete response; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival.

1. Shi Q, et al. *J Clin Oncol* 2025;43(11):1289-301. 2. Landgren O, et al. *Blood* 2024;144(4):359-67.

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MRD as an Early Endpoint: Regulatory Opinions

- The Oncologic Drugs Advisory Committee **(ODAC) for FDA** unanimously voted (12-0) in favor of using MRD as an **early endpoint for accelerated approval** in multiple myeloma clinical trials (April 12, 2024)[1]
- The Committee for Medicinal Products for Human Use **(CHMP) from EMA**, stated "CHMP agrees that, depending on the setting, a role for **MRDnegCR as an endpoint to support (conditional) approval** of a compound while the obligation to demonstrate long-term benefit remains, can be envisaged. This implies that the trials should be adequately planned…" (scientific advice letter dated May 5, 2025)[2]

- *When evaluating the approval of a novel therapeutic agent, it is essential not only to demonstrate a survival benefit but also to show an acceptable safety profile*
- Regulatory authorities **require evidence** that achieving the deepest level of response, defined as MRD negativity, *does not occur at the cost of increased* adverse events or a deterioration in PROs
- **Currently, there is a lack of evidence regarding the impact of achieving MRD negativity on HRQoL in NDMM patients**

CR, complete response; EMA, European Medicines Agency; FDA, Food and Drug Administration; HRQoL, health-related quality of life; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

1. US Food and Drug Administration. Accessed September 4, 2025. https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024. 2. International Myeloma Foundation. Accessed September 4, 2025. https://www.myeloma.org/news-events/multiple-myeloma-news/imf-proudly-announces-ema-chmp-positive-qualification-advice-i2teamm-novel-biomarker-procedure.

PERSEUS and CEPHEUS PRO and Safety: Methods

- Patients were randomized 1:1 to receive DVRd induction/consolidation + DR maintenance vs VRd induction/consolidation + R maintenance (PERSEUS) or to receive DVRd vs VRd (CEPHEUS)
- **MRD-negativity rate** (10^{-5} and ≥CR) was a key **secondary** (PERSEUS) or **primary** (CEPHEUS) endpoint
  - Patients with indeterminate results or those achieving MRD negativity but not ≥CR were considered MRD positive
- **PROs** were evaluated at baseline, and day 1, cycles 1-3, pre-ASCT, cycle 5, cycle 7 and then Q12W (PERSEUS) or day 1, cycles 1-8 and every third cycle (CEPHEUS)
- PROs included concepts from the European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 **(EORTC QLQ-C30)**
  - Key outcomes included global health status

TEAEs were graded with NCI-CTCAE v.5

- Exposure-adjusted incidence rates were calculated using the number of patients with the event divided by the 100 patient-months at risk for that event. The number of months at risk was a sum of exposure time from the first dose date up to the first onset date of the event among all patients. For patients without the event, this was censored to the last date of exposure

ASCT, autologous stem cell transplant; CR, complete response; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PRO, patient-reported outcome; Q12W, every 12 weeks; R, lenalidomide; TEAE, treatment-emergent adverse event; VRd, bortezomib, lenalidomide, and dexamethasone.

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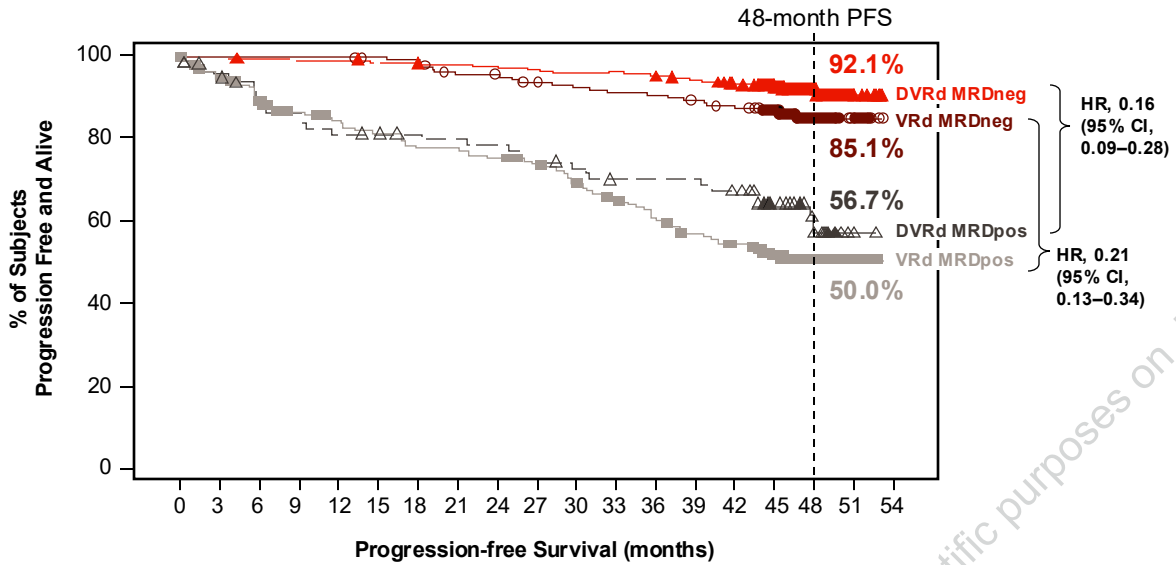
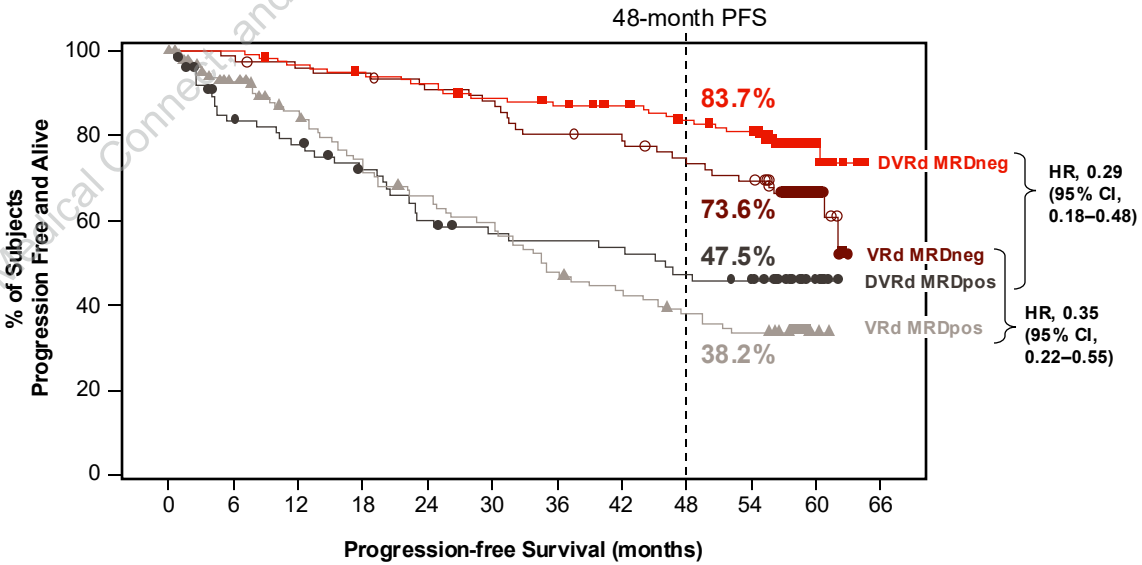
Achievement of MRD Negativity (10^{-5} and ≥CR) and Impact on PFS in PERSEUS and CEPHEUS

PERSEUS



Subjects at risk																			
DVRd MRD Negative	267	267	265	264	264	260	259	258	256	255	253	253	250	246	240	194	76	10	0
DVRd MRD Positive	88	78	70	65	63	62	59	58	57	54	52	49	49	49	46	32	14	1	0
VRd MRD Negative	168	168	168	168	168	166	165	157	156	152	149	147	146	143	139	115	44	10	0
VRd MRD Positive	186	167	153	143	136	131	126	126	122	118	109	100	92	85	80	60	23	3	0

CEPHEUS



Subjects at risk												
DVRd MRD Negative	120	120	115	112	109	104	101	98	92	88	24	0
DVRd MRD Positive	77	60	55	48	40	36	35	34	30	27	9	0
VRd MRD Negative	78	77	74	73	69	67	61	59	54	51	18	0
VRd MRD Positive	120	97	83	70	62	56	44	39	34	30	3	0

Patients achieving MRD negativity had improved PFS vs those who remained MRD positive

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

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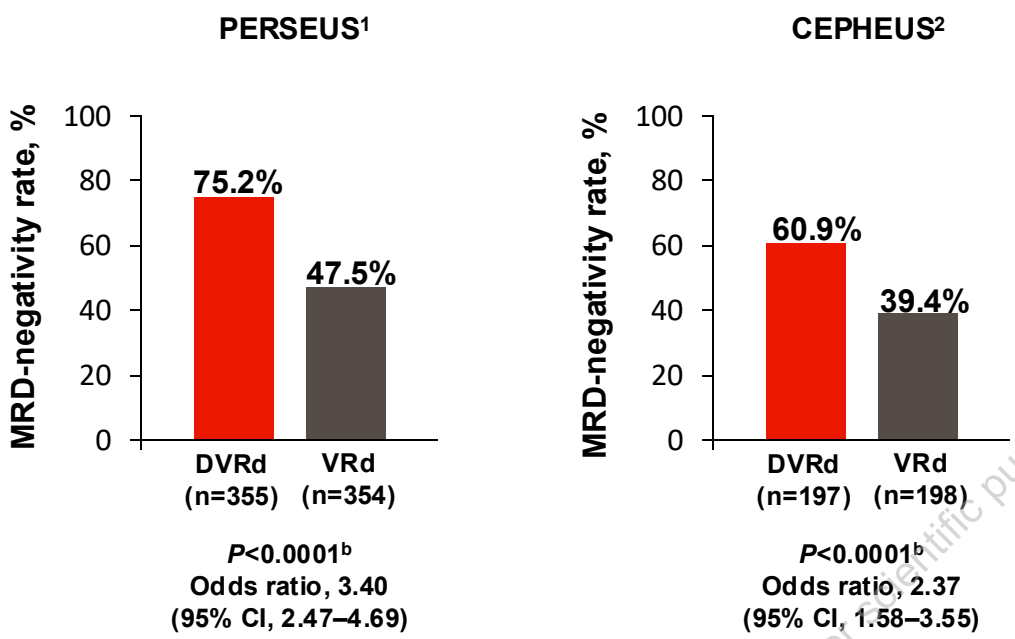
PERSEUS and CEPHEUS: MRD-Negativity Rates (10^{-5} and ≥CR) and Median Treatment Duration

Overall MRD-negativity (10^{-5} and ≥CR) rate[a]



Median treatment duration of regimens, months		MRD Negative ≥CR	MRD Positive
PERSEUS *Median follow-up*, 47.5 mo *Median age*, 60 y (range, 31–70)	DVRd	46.0[c]	41.3
	VRd	45.9	30.9
CEPHEUS *Median follow-up*, 58.7 mo *Median age*, 70 y (range, 31–80)	DVRd	57.5	22.5
	VRd	56.6	21.7

Median treatment duration was longer in patients who achieved MRD negativity vs MRD-positive patients in PERSEUS and CEPHEUS

[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]In PERSEUS, lenalidomide maintenance was continued until progression. At the time of clinical cutoff, 207 of 322 patients who had entered the maintenance phase in the DVRd group had discontinued daratumumab monotherapy in accordance with the protocol (ie, after they had received ≥24 months of maintenance therapy and attained ≥CR and sustained MRD-negative status for ≥12 months.
CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; mo, month; MRD, minimal residual disease; PRO, patient-reported outcomes; VRd, bortezomib, lenalidomide, and dexamethasone; y, year.
1. Sonneveld P, et al. *N Engl J Med* 2024;390(4):301-13. 2. Usmani SZ, et al. *Nat Med* 2025;31(4):1195-202.

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PERSEUS and CEPHEUS: Exposure-Adjusted Safety Outcomes in the DVRd Arms

Because of the difference in treatment duration between MRD-negative and MRD-positive patients, we assessed exposure-adjusted safety outcomes per 100 patient-months

	PERSEUS DVRd		CEPHEUS DVRd	
	MRD Negative ≥CR	MRD Positive	MRD Negative ≥CR	MRD Positive
Any TEAE	156.82	165.12	119.64	235.78
Grade 3/4 TEAE	11.89	17.65	11.34	13.15
Serious TEAE	2.21	3.21	2.99	3.99
TEAE leading to discontinuation	0.19	0.35	0.10	0.38
TEAE with outcome of death	0.07	0.19	0.25	0.76
Neutropenia, Grade 3/4	3.06	4.39	1.51	2.15
Infections, Grade 3/4	1.03	1.67	0.98	1.92

Despite prolonged exposure, TEAEs consistently favored patients who achieved MRD negativity vs MRD-positive patients in the DVRd arm across analyses in PERSEUS and CEPHEUS

CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; EAIR, exposure-adjusted incidence rate; MRD, minimal residual disease; TEAE, treatment-emergent adverse event.

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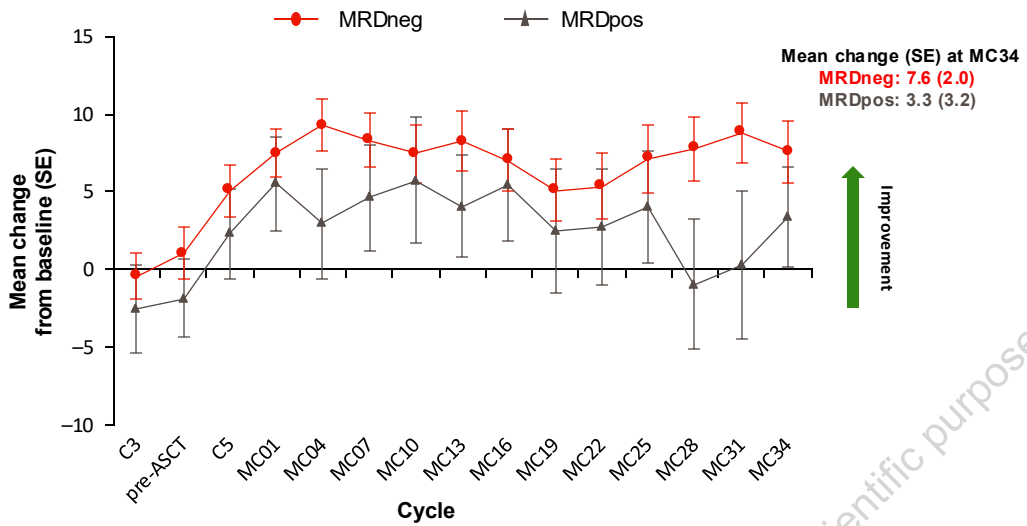
PRO Scores in the DVRd Arms: EORTC QLQ-C30 Global Health Status

PERSEUS

Mean change in EORTC QLQ-C30 GHS scores from baseline over time

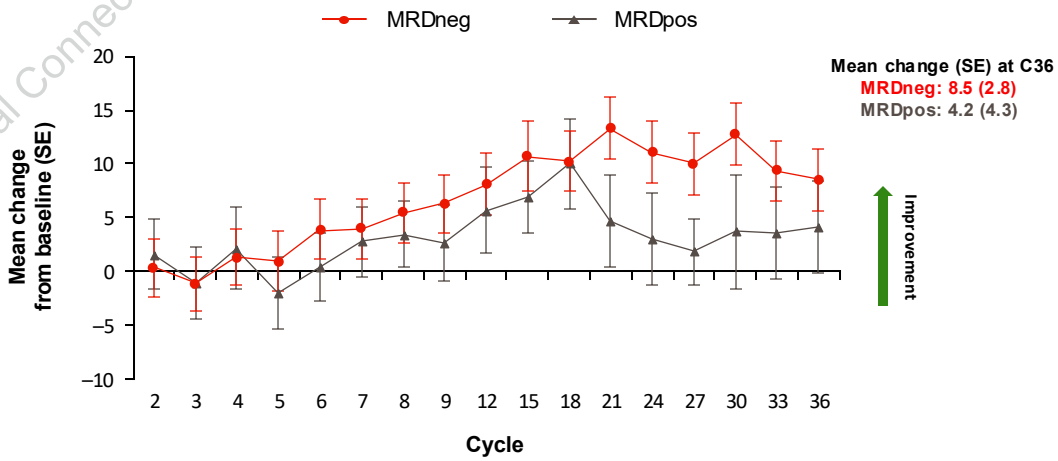


No. of patients

MRDneg	242	227	227	227	218	222	219	224	210	215	195	181	183	171	155	
MRDpos	71	63	58	56	54	47	45	47	46	41	42	37	35	34	30	

CEPHEUS

Mean change in EORTC QLQ-C30 GHS scores from baseline over time



No. of patients

MRDneg	103	105	104	101	101	101	100	98	94	87	83	85	86	87	83	74	79
MRDpos	61	60	53	54	54	53	51	50	41	41	39	39	35	27	27	28	28

PRO scores were similar for patients in the DVRd arms who achieved MRD negativity vs MRD-positive patients

[a]At maintenance cycle 34 (PERSEUS) and at cycle 36 (CEPHEUS).
DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30; GHS, global health status; MRD, minimal residual disease; neg, negative; pos, positive; PRO, patient-reported outcomes.

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PROs and Safety in Patients With NDMM Achieving MRD Negativity: Conclusions

- This is the **first report** showing that, for NDMM patients receiving DVRd-based standard-of-care treatment, achieving **MRD negativity** (compared with those who do not) not only improves PFS, but is also associated with:
  - favorable exposure-adjusted safety outcomes
  - no detriment to patient-reported HRQoL

- Patients achieving MRD negativity stayed on treatment longer and maintained HRQoL despite this prolonged exposure

Overall, these data help reassure physicians that the pursuit of MRD negativity in patients with NDMM does not adversely impact safety or HRQoL

DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HRQoL, health-related quality of life; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; PRO, patient-reported outcome.

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PERSEUS and CEPHEUS PRO and Safety: Acknowledgments

- Patients who participated in these studies and their families
- Staff members at the study sites
- Data and safety monitoring committee
- The European Myeloma Network (EMN) and Johnson & Johnson
- EMN acknowledges the valuable contributions and participation of the National Myeloma Study Groups of all participating countries in Europe and Australia
- Medical writing support was provided by Erin Burns-Tidmore, PhD, of Eloquent, part of Envision Spark, an Envision Medical Communications agency, a part of Envision Pharma Group, and funded by Johnson & Johnson

- PERSEUS was sponsored by EMN in collaboration with Johnson & Johnson
- CEPHEUS was sponsored by Johnson & Johnson

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PERSEUS and CEPHEUS: Exposure-Adjusted Safety Outcomes in the VRd Arms

Because of the difference in treatment duration between MRD-negative and MRD-positive patients, we assessed exposure-adjusted safety outcomes per 100 patient-months

	PERSEUS VRd		CEPHEUS VRd	
	MRD Negative ≥CR	MRD Positive	MRD Negative ≥CR	MRD Positive
Any TEAE	68.60	129.55	124.04	230.05
Grade 3/4 TEAE	7.19	9.85	7.15	14.52
Serious TEAE	1.55	3.02	3.04	4.45
TEAE leading to discontinuation	0.49	0.84	0.25	0.68
TEAE with outcome of death	0.04	0.26	0.22	0.40
Neutropenia, Grade 3/4	2.08	2.68	0.93	1.29
Infections, Grade 3/4	0.69	1.47	0.91	1.42

Despite prolonged exposure, TEAEs consistently favored patients who achieved MRD negativity vs MRD-positive patients in the VRd arm across analyses in PERSEUS and CEPHEUS

CR, complete response; MRD, minimal residual disease; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event; VRd, bortezomib, lenalidomide, and dexamethasone.

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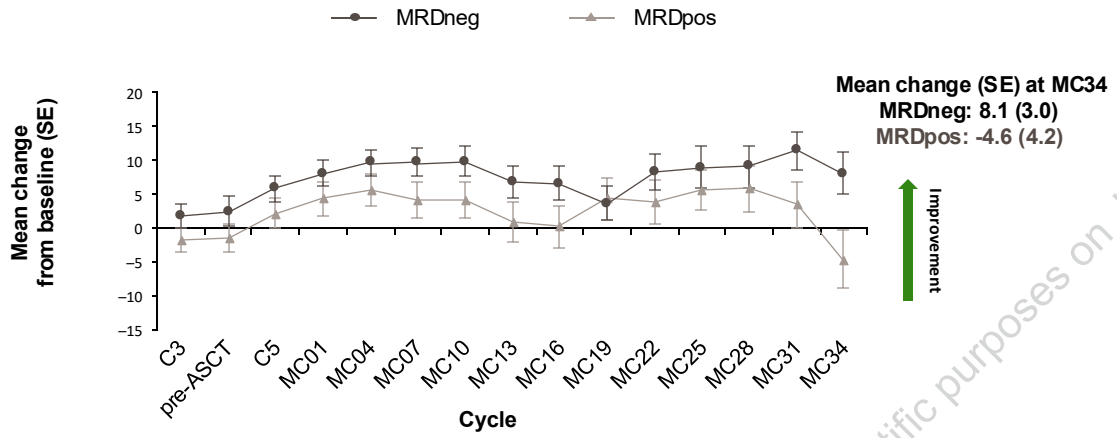
PERSEUS

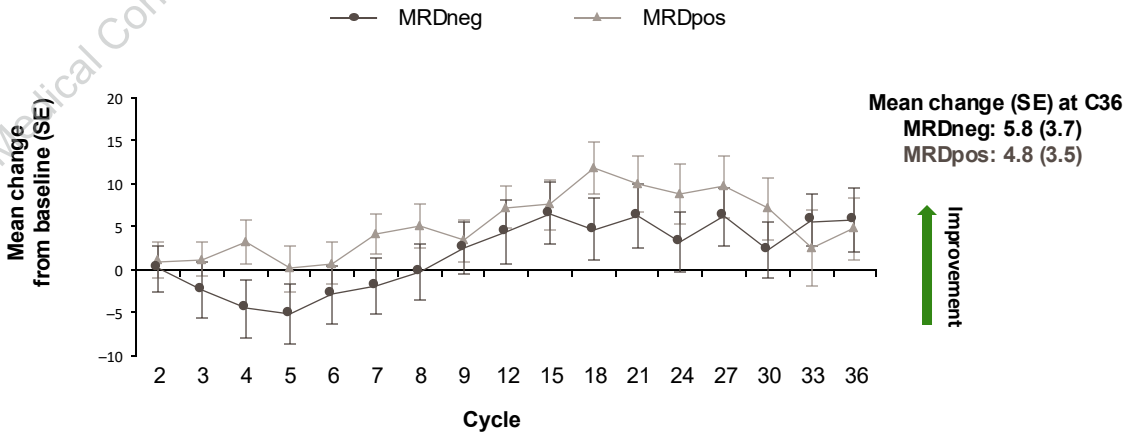
Mean change in EORTC QLQ-C30 GHS scores from baseline over time



No. of patients															
MRDneg	158	150	152	152	152	145	135	121	120	115	119	106	94	92	78
MRDpos	153	137	122	115	108	96	90	88	75	71	66	57	50	44	36

CEPHEUS

Mean change in EORTC QLQ-C30 GHS scores from baseline over time



No. of patients																	
MRDneg	67	67	70	66	69	67	65	66	58	52	53	51	52	50	47	51	46
MRDpos	97	95	91	91	91	86	84	81	70	63	57	53	47	45	46	42	42

PRO scores were similar for patients in the VRd arms who achieved MRD negativity vs MRD-positive patients

[a]At maintenance cycle 34 (PERSEUS) and at cycle 36 (CEPHEUS).
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30; GHS, global health status; MRD, minimal residual disease; neg, negative; pos, positive; PRO, patient-reported outcomes; VRd, bortezomib, lenalidomide, and dexamethasone.

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