Daratumumab (DARA SC)/Bortezomib/Lenalidomide/ Dexamethasone (D-VRd) With D-R Maintenance in Transplant-eligible (TE) Newly Diagnosed Myeloma (NDMM): PERSEUS Cytogenetic Risk Analysis*

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Meletios A Dimopoulos[1], Pieter Sonneveld[2], Paula Rodríguez-Otero[3], Hang Quach[4], P Joy Ho[5], Meral Beksac[6], Cyrille Hulin[7], Elisabetta Antonioli[8], Xavier Leleu[9], Silvia Mangiacavalli[10], Aurore Perrot[11], Michele Cavo[12], Angelo Belotti[13], Annemiek Broijl[2], Francesca Gay[14], Roberto Mina[14], Inger S Nijhof[15,16], Niels WCJ van de Donk[15], Eirini Katodritou[17], Anna Sitthi-Amorn[18], Carla J de Boer[19], Robin Carson[18], Joan Bladé[20], Philippe Moreau[21], Mario Boccadoro[22]

[1]National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Hematology, EMN/Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [3]Department of Hematology, Cancer Center Clínica Universidad de Navarra, Pamplona, Navarra, Spain; [4]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [5]Institute of Haematology, Royal Prince Alfred Hospital and University of Sydney, Camperdown, NSW, Australia; [6]Ankara University, Ankara, Turkey; [7]Department of Hematology, Hôpital Haut Lévêque, University Hospital, Pessac, France; [8]Department of Hematology, Careggi Hospital and University of Florence, Firenze, Italy; [9]University of Poitiers, CHU and Inserm 1313, Poitiers, France; [10]Hematology Division, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; [11]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [12]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [13]Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; [14]Division of Hematology 1, AOU Città della Salute e della Scienza di Torino, and Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; [15]Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [16]Department of Hematology, St Antonius Hospital, Nieuwegein, The Netherlands; [17]Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece; [18]Janssen Research & Development, LLC, Spring House, PA, USA; [19]Janssen Research & Development, LLC, Leiden, The Netherlands; [20]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; and GEM/PETHEMA; [21]Hematology Department, University Hospital Hôtel-Dieu, Nantes, France; [22]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

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Disclosure Statement: Meletios A Dimopoulos, MD

- **Honoraria:** Amgen, Sanofi, Regeneron, Menarini, Takeda, GSK, Bristol Myers Squibb, Janssen, BeiGene, Swixx, AstraZeneca

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PERSEUS: Introduction

In the primary analysis of the phase 3 PERSEUS study, D-VRd/ASCT + D-R maintenance significantly improved PFS and increased depth of response, including ≥CR, vs VRd/ASCT + R maintenance alone in TE patients with NDMM at a median follow-up of 47.5 months[1]

- Overall and sustained MRD-negativity rates were significantly higher with D-VRd + D-R maintenance vs VRd + R maintenance[1,2]
  - Overall (10^{-5}): 75.2% vs 47.5% (*P* <0.0001)
  - Overall (10^{-6}): 65.1% vs 32.2% (*P* <0.0001)
  - Sustained (≥12 months; 10^{-5}): 64.8% vs 29.7% (*P* <0.0001)
  - Sustained (≥12 months; 10^{-6}): 47.3% vs 18.6% (*P* <0.0001)
- Consistent benefits were observed across subgroups, including in patients with HRCAs (ie, del[17p], t[4;14], or t[14;16])

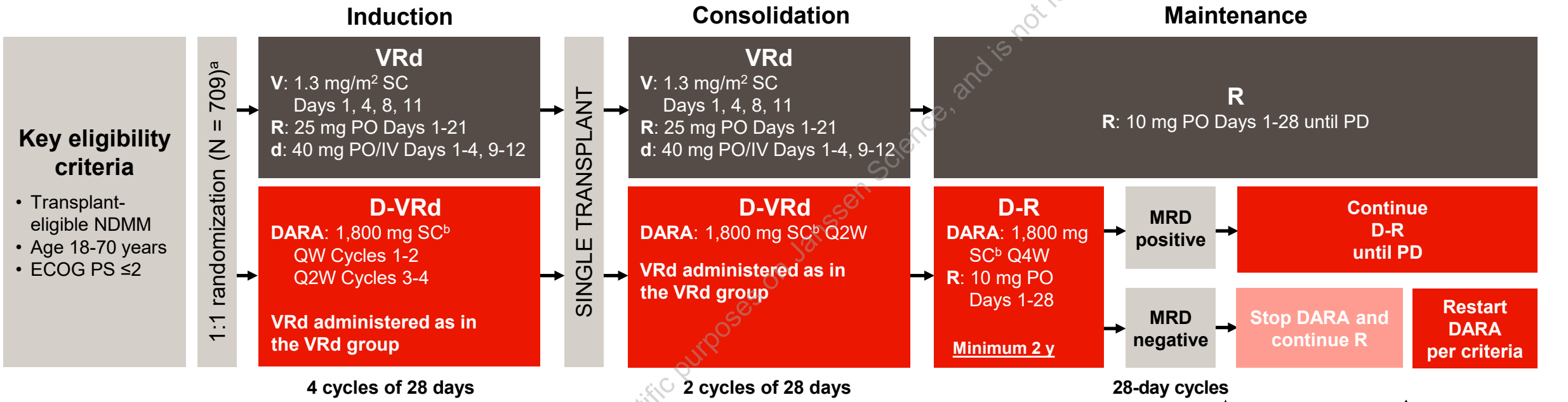
Historically, patients with HRCAs often have a poor prognosis and experience poor disease outcomes[3]

DARA has shown benefit in NDMM patients with HRCAs, including gain/amp(1q21),[4-6] and here we confirm these results in PERSEUS, a large phase 3 study in TE NDMM

We report an expanded analysis of PERSEUS clinical outcomes (PFS, overall MRD negativity, and sustained MRD negativity) based on R2-ISS disease stage and the presence of HRCAs, including gain(1q21) and amp(1q21)

D-VRd, daratumumab (with recombinant human hyaluronidase for subcutaneous injection) plus bortezomib/lenalidomide/dexamethasone; ASCT, autologous stem cell transplant; D-R, daratumumab (with recombinant human hyaluronidase for subcutaneous injection) plus lenalidomide; PFS, progression-free survival; CR, complete response; VRd, bortezomib/lenalidomide/dexamethasone; R, lenalidomide; TE, transplant eligible; NDMM, newly diagnosed multiple myeloma; MRD, minimal residual disease; HRCA, high-risk cytogenetic abnormality; DARA, daratumumab; R2-ISS, second revised International Staging System. 1. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313. 2. Rodriguez-Otero P, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA. 3. Hanamura I. *Int J Hematol*. 2022;115(6):762-777. 4. Callander NS, et al. *Blood Cancer J*. 2024;14(1):69. 5. Fu W, et al. *Ann Hematol*. 2024; https://doi.org/10.1007/s00277-024-05958-8. 6. Moreau P, et al. Presented at: 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA, USA.

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate (10^{-5}),[d] OS

Stop DARA therapy after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity (10^{-5})

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

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.

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; OS, overall survival; ITT, intent to treat; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response.
[a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc.). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

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PERSEUS: Assessments and Definitions

PFS (primary endpoint) was defined as the time from the date of randomization to the date of first disease progression (as per IMWG response criteria[1]) or death, whichever occurred first

- PFS was compared between treatment groups using a log-rank test; the Kaplan–Meier method was used to estimate PFS distributions
- Treatment effect (HR) and corresponding 95% CIs were estimated using a Cox regression model, with treatment as the sole variable

Overall MRD-negativity rate was defined as the proportion of patients who achieved MRD negativity (at or below 10^{-5}) and ≥CR at any time during the study

- Sustained MRD negativity was defined as 2 consecutive MRD negative results (at or below 10^{-5}) ≥12 months apart without any MRD positive (10^{-4} or higher) results in between
- MRD was assessed using bone marrow aspirates by next-generation sequencing (clonoSEQ® Assay, Version 2.0; Adaptive Biotechnologies)
- Treatment effect (OR) and corresponding 95% CIs were estimated using a Mantel–Haenszel estimation

HR, hazard ratio; CI, confidence interval; OR, odds ratio.

1. Rajkumar SV, et al. *Blood* 2011;117:4691-4695.

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PERSEUS: Cytogenetic Risk Subgroups

The following cytogenetic risk subgroups were explored:

- R2-ISS
- Standard risk – per protocol: none of del(17p), t(4;14), or t(14;16)
- High risk – per protocol: ≥1 of del(17p), t(4;14), or t(14;16)
- Revised standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21)
- Revised high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21)
  - 1 revised HRCA
  - ≥2 revised HRCAs
- Gain(1q21): 3 copies of chromosome 1q21, with or without other HRCAs
- Amp(1q21): 4 or more copies of chromosome 1q21, with or without other HRCAs
- Gain(1q21) or amp(1q21): presence of gain(1q21) or amp(1q21), with or without other HRCAs
- Isolated gain(1q21): 3 copies of chromosome 1q21, without any other HRCAs
- Isolated amp(1q21): 4 or more copies of chromosome 1q21, without any other HRCAs

Cytogenetic risk was centrally assessed by FISH[a]

FISH, fluorescence in situ hybridization.
[a]Patients were considered positive for a chromosome abnormality when test result met or exceeded the threshold established by the central laboratory.

PERSEUS: Baseline Risk Characteristics

In total, 709 patients were randomized

- D-VRd, n = 355; VRd, n = 354
- Patient demographic and baseline characteristics were well balanced between groups and have been previously presented[1]

Characteristic	D-VRd (n = 355)	VRd (n = 354)
ISS disease stage, n/N (%)		
I	186/355 (52.4)	178/353 (50.4)
II	114/355 (32.1)	125/353 (35.4)
III	55/355 (15.5)	50/353 (14.2)
Cytogenetic abnormalities, n (%)		
del(17p)	36 (10.1)	34 (9.6)
t(4;14)	33 (9.3)	38 (10.7)
t(14;16)	11 (3.1)	14 (4.0)
Gain(1q21)[a]	59 (16.6)	71 (20.1)
Amp(1q21)[b]	28 (7.9)	36 (10.2)
Cytogenetic risk,[c] n (%)		
Standard	264 (74.4)	266 (75.1)
High	76 (21.4)	78 (22.0)
Indeterminate	15 (4.2)	10 (2.8)
Revised cytogenetic risk,[d] n (%)		
Revised standard	174 (49.0)	167 (47.2)
Revised high	130 (36.6)	148 (41.8)
Indeterminate	51 (14.4)	39 (11.0)
R2-ISS disease stage, n (%)		
Low (I)	116 (32.7)	114 (32.2)
Low-intermediate (II)	111 (31.3)	106 (29.9)
Intermediate-high (III)	108 (30.4)	115 (32.5)
High (IV)	20 (5.6)	19 (5.4)

[a]Gain(1q21) was defined as the presence of 3 copies of chromosome 1q21.
[b]Amp(1q21) was defined as the presence of 4 or more copies of chromosome 1q21.
[c]Cytogenetic risk was based on FISH; high risk was defined as the presence of del(17p), t(4;14), or t(14;16).
[d]Revised high risk was defined as presence of del(17p), t(4;14), t(14;16), gain(1q21), or amp(1q21).

1. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313.

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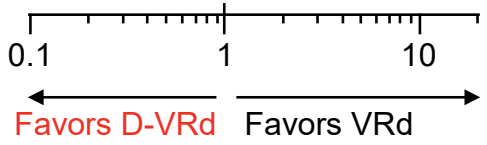
PERSEUS: Subgroup Analysis of PFS Based on Cytogenetic Risk Status (ITT)

	D-VRd		VRd			
	n/N	Median PFS (mo)	n/N	Median PFS (mo)	HR (95% CI)	*P* value
Standard risk	25/264	NE	62/266	NE	0.35 (0.22–0.56)	<0.0001
High risk	24/76	NE	38/78	44.1	0.59 (0.36–0.99)	0.0439
Revised standard risk	12/174	NE	35/167	NE	0.29 (0.15–0.56)	0.0001
Revised high risk	33/130	NE	62/148	NE	0.53 (0.35–0.81)	0.0027
Gain(1q21)	15/59	NE	26/71	NE	0.62 (0.33–1.18)	0.1400
Amp(1q21)	6/28	NE	17/36	46.7	0.37 (0.15–0.94)	0.0306
Gain(1q21) or amp(1q21)	21/87	NE	43/107	NE	0.52 (0.31–0.88)	0.0133
Isolated gain(1q21)	8/37	NE	15/47	NE	0.57 (0.24–1.36)	0.2004
Isolated amp(1q21)	1/17	NE	9/23	NE	0.11 (0.01–0.87)	0.0115
1 revised HRCA	21/97	NE	43/110	NE	0.47 (0.28–0.79)	0.0035
≥2 revised HRCAs	12/33	NE	19/38	44.1	0.73 (0.35–1.50)	0.3878



PFS favored D-VRd followed by D-R maintenance across all cytogenetic risk subgroups

NE, not evaluable.
Isolated gain(1q21) or isolated amp(1q21) was defined as the presence of 3 copies or ≥4 copies of chromosome 1q21, respectively, without any other HRCAs.

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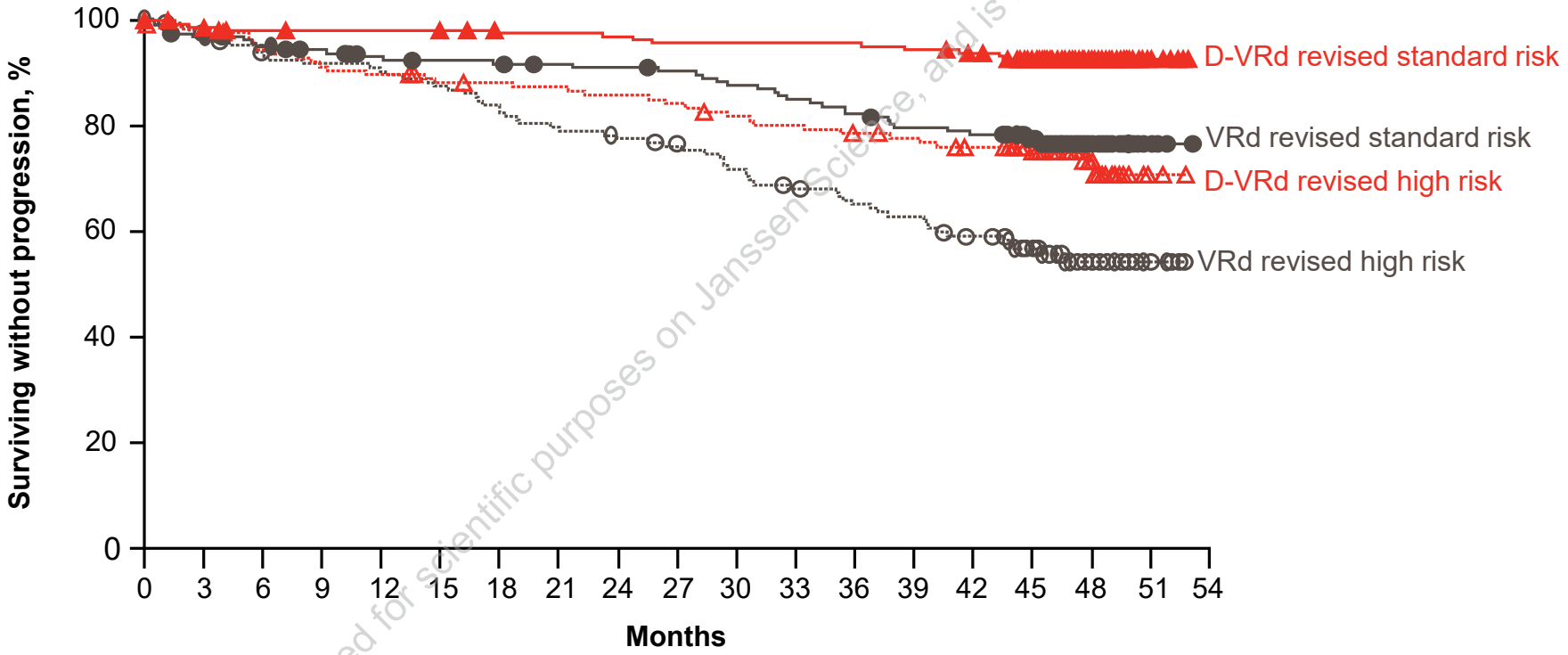
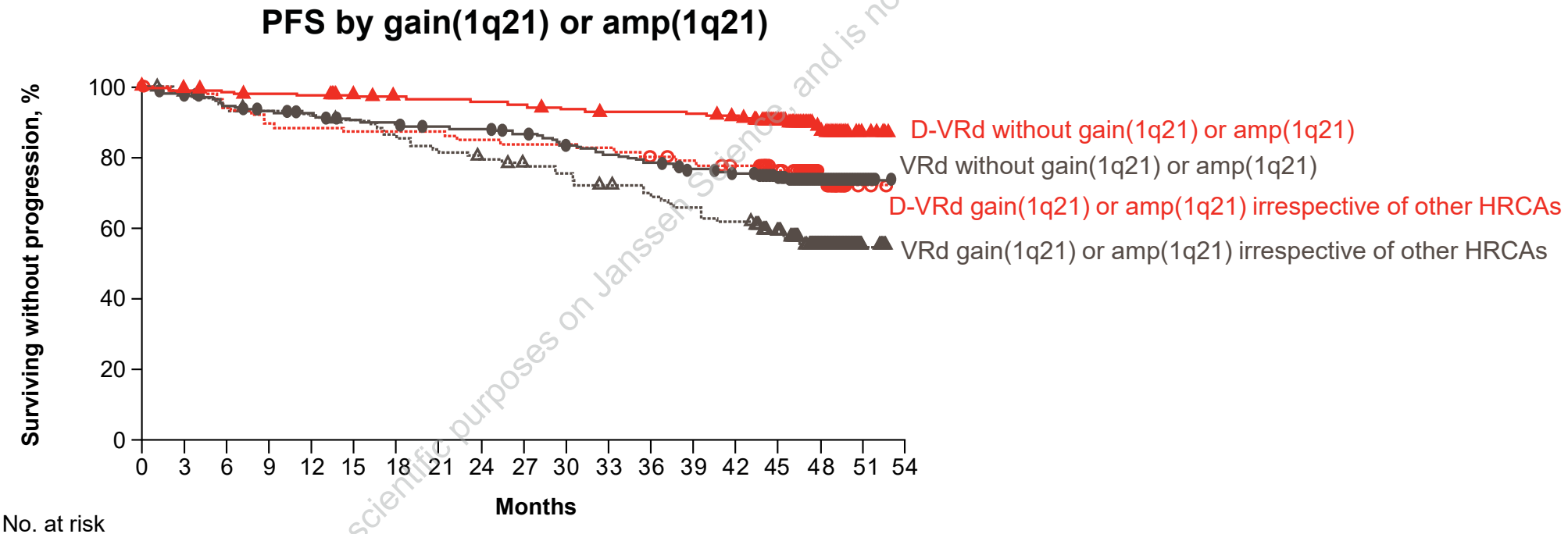
PERSEUS: Subgroup Analysis of PFS Based on Revised[a] Cytogenetic Risk Status (ITT)



No. at risk																			
VRd revised standard risk	167	157	152	148	143	141	140	138	137	135	131	127	123	118	116	96	36	6	0
D-VRd revised standard risk	174	167	163	162	162	162	159	158	157	155	155	155	155	153	149	124	52	7	0
VRd revised high risk	148	139	132	129	127	123	118	112	109	105	98	92	87	84	77	64	22	4	0
D-VRd revised high risk	130	127	121	117	115	111	110	109	107	105	101	99	96	94	90	76	31	2	0

[a]Revised standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21). Revised high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).

PERSEUS: Subgroup Analysis of PFS Based on Chromosome 1q21 Status



No. at risk																			
VRd without gain or amp	247	234	226	217	212	206	204	200	198	193	185	178	173	166	161	127	52	10	0
D-VRd without gain or amp	268	260	255	253	252	248	244	242	241	238	234	232	232	230	224	175	70	9	0
VRd gain or amp irrespective of other HRCAs	107	101	95	94	92	91	87	83	80	77	73	69	65	62	58	48	15	3	0
D-VRd gain or amp irrespective of other HRCAs	87	85	80	76	75	74	74	74	72	71	71	70	67	65	62	51	20	2	0

DARA improved outcomes in patients with gain(1q21) or amp(1q21)

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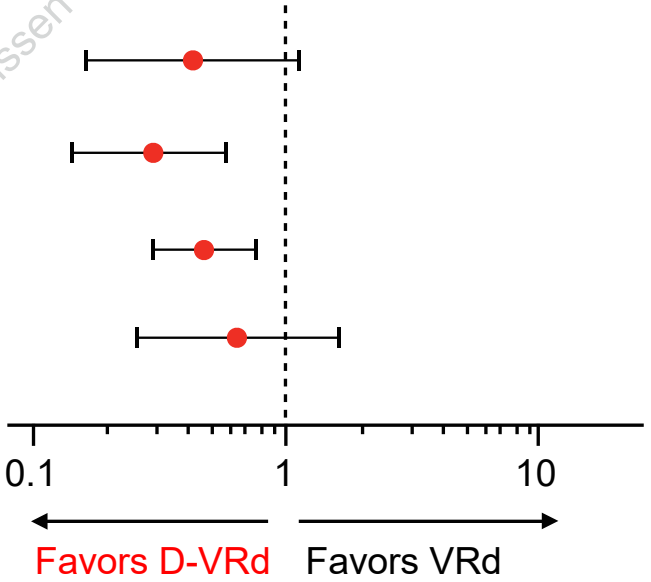
PERSEUS: Subgroup Analysis of PFS Based on R2-ISS Disease Stage

	D-VRd		VRd		
	n/N	Median PFS (mo)	n/N	Median PFS (mo)	HR (95% CI)
Low (I)	6/116	NE	13/114	NE	0.42 (0.16-1.11)
Low-intermediate (II)	11/111	NE	30/106	NE	0.29 (0.14-0.57)
Intermediate-high (III)	25/108	NE	50/115	NE	0.46 (0.29-0.75)
High (IV)	8/20	NE	10/19	39.8	0.63 (0.25-1.61)



Subgroup analysis of PFS favored D-VRd followed by D-R maintenance regardless of R2-ISS disease stage

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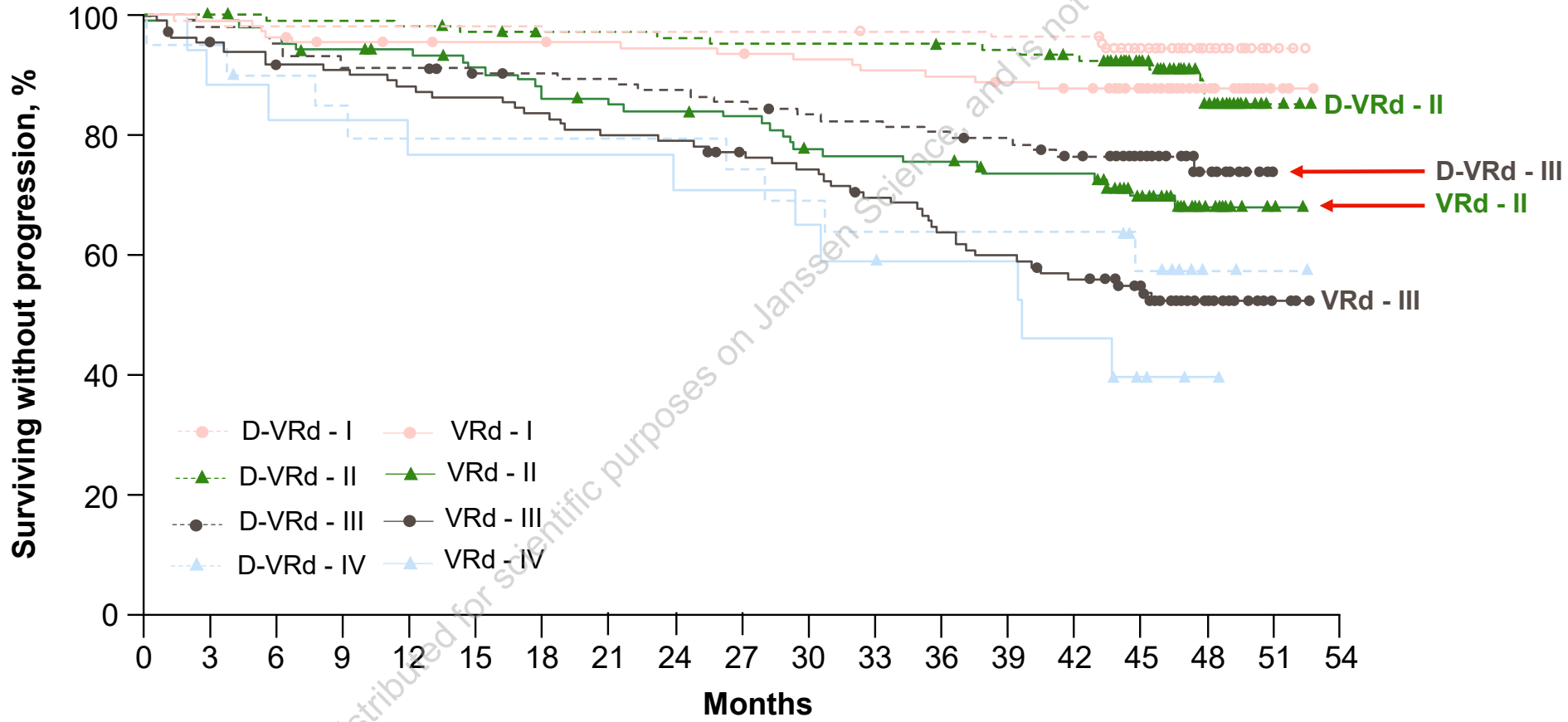
PERSEUS: Subgroup Analysis of PFS Based on R2-ISS Disease Stage (ITT)



The addition of DARA extended PFS regardless of R2-ISS disease stage and was more pronounced for R2-ISS disease stage II and III

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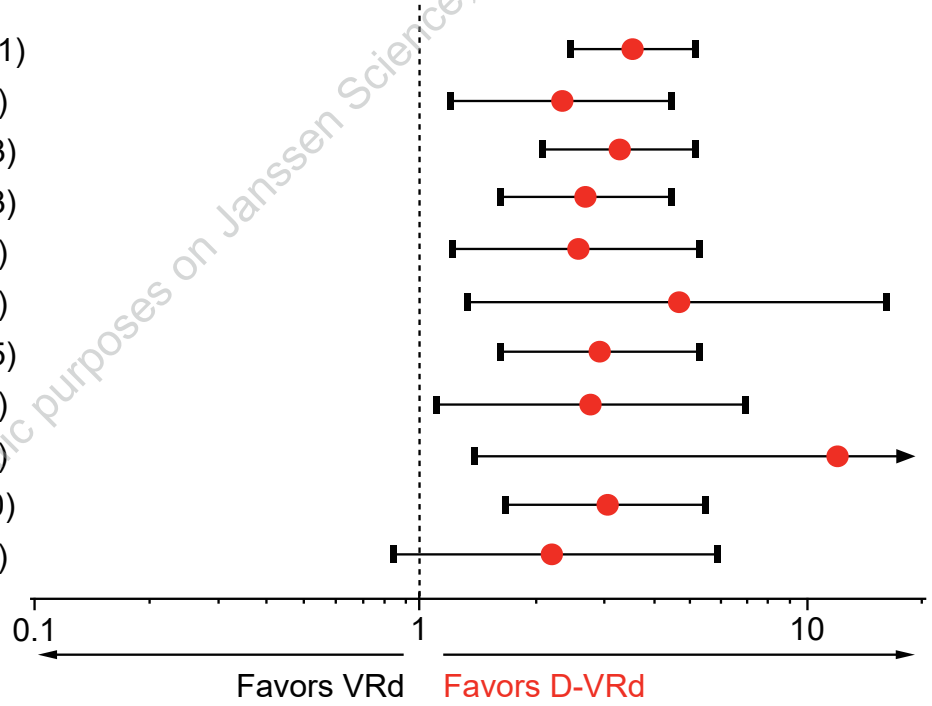
PERSEUS: Subgroup Analysis of MRD Negativity (10^{-5}) Based on Cytogenetic Risk Status

Subgroup analysis of MRD negativity (10^{-5}) with ≥CR

	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)
Standard risk	204/264 (77.3)	128/266 (48.1)	3.67 (2.52–5.33)
High risk	52/76 (68.4)	37/78 (47.4)	2.40 (1.24–4.63)
Revised standard risk	131/174 (75.3)	79/167 (47.3)	3.39 (2.14–5.37)
Revised high risk	95/130 (73.1)	73/148 (49.3)	2.79 (1.68–4.62)
Gain(1q21)	41/59 (69.5)	33/71 (46.5)	2.62 (1.27–5.41)
Amp(1q21)	24/28 (85.7)	20/36 (55.6)	4.80 (1.38–16.69)
Gain(1q21) or amp(1q21)	65/87 (74.7)	53/107 (49.5)	3.01 (1.63–5.56)
Isolated gain(1q21)	27/37 (73.0)	23/47 (48.9)	2.82 (1.12–7.10)
Isolated amp(1q21)	16/17 (94.1)	13/23 (56.5)	12.31 (1.39–109.10)
1 revised HRCA	73/97 (75.3)	55/110 (50.0)	3.04 (1.68–5.51)
≥2 revised HRCAs	22/33 (66.7)	18/38 (47.4)	2.22 (0.85–5.83)



Subgroup analysis of MRD negativity (10^{-5}) based on cytogenetic risk status favored D-VRd followed by D-R maintenance

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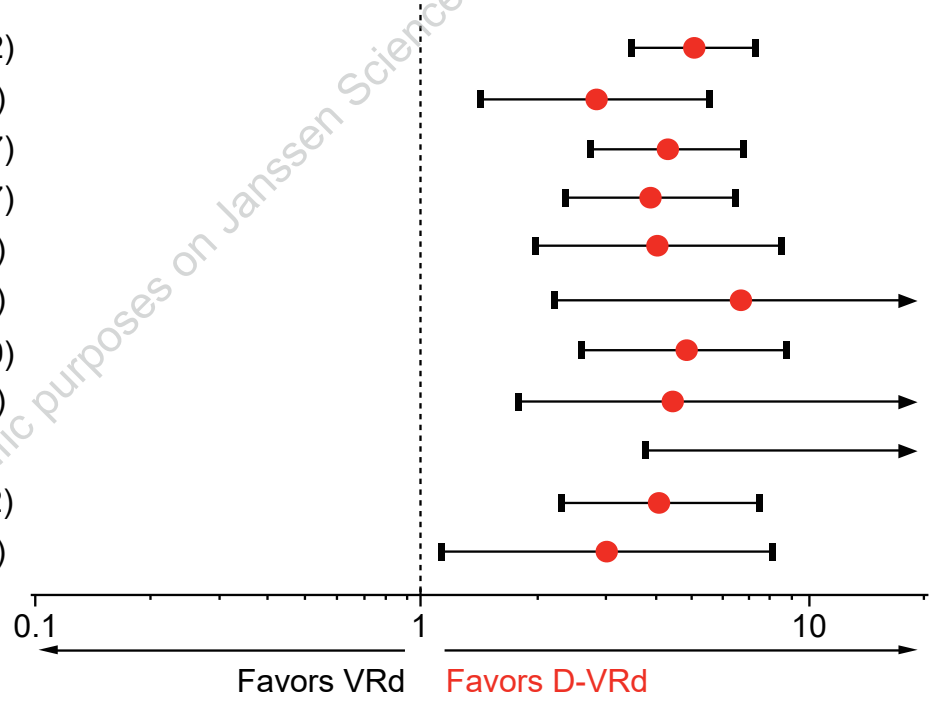
PERSEUS: Subgroup Analysis of Sustained MRD Negativity (10^{-5}) Based on Cytogenetic Risk Status

Subgroup analysis of sustained MRD negativity (10^{-5}) for ≥12 months

	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)
Standard risk	183/264 (69.3)	83/266 (31.2)	4.98 (3.45–7.20)
High risk	37/76 (48.7)	20/78 (25.6)	2.75 (1.40–5.42)
Revised standard risk	115/174 (66.1)	53/167 (31.7)	4.19 (2.67–6.59)
Revised high risk	77/130 (59.2)	41/148 (27.7)	3.79 (2.30–6.26)
Gain(1q21)	37/59 (62.7)	21/71 (29.6)	4.00 (1.92–8.34)
Amp(1q21)	20/28 (71.4)	10/36 (27.8)	6.50 (2.17–19.48)
Gain(1q21) or amp(1q21)	57/87 (65.5)	31/107 (29.0)	4.66 (2.54–8.56)
Isolated gain(1q21)	25/37 (67.6)	15/47 (31.9)	4.44 (1.77–11.17)
Isolated amp(1q21)	15/17 (88.2)	6/23 (26.1)	21.25 (3.71–121.61)
1 revised HRCA	60/97 (61.9)	31/110 (28.2)	4.13 (2.31–7.41)
≥2 revised HRCAs	17/33 (51.5)	10/38 (26.3)	2.97 (1.10–8.04)



Subgroup analysis of sustained MRD negativity (10^{-5}) based on cytogenetic risk status favored D-VRd followed by D-R maintenance

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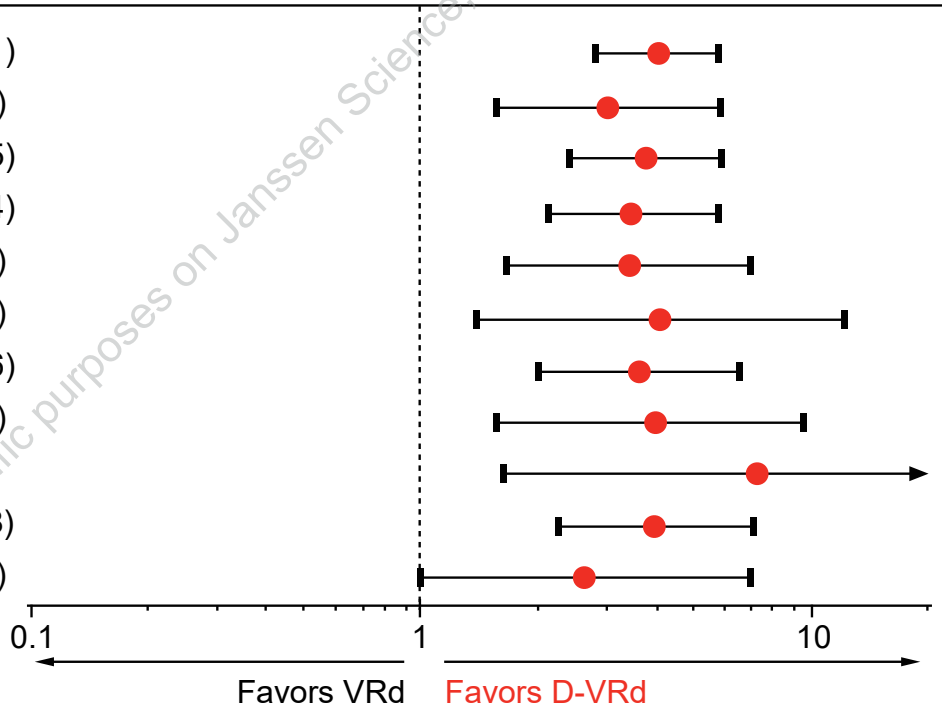
PERSEUS: Subgroup Analysis of MRD Negativity (10^{-6}) Based on Cytogenetic Risk Status

Subgroup analysis of MRD negativity (10^{-6}) with ≥CR

	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)
Standard risk	177/264 (67.0)	88/266 (33.1)	4.12 (2.87–5.91)
High risk	44/76 (57.9)	24/78 (30.8)	3.09 (1.60–6.00)
Revised standard risk	115/174 (66.1)	56/167 (33.5)	3.86 (2.47–6.05)
Revised high risk	82/130 (63.1)	48/148 (32.4)	3.56 (2.17–5.84)
Gain(1q21)	36/59 (61.0)	22/71 (31.0)	3.49 (1.69–7.20)
Amp(1q21)	21/28 (75.0)	15/36 (41.7)	4.20 (1.42–12.39)
Gain(1q21) or amp(1q21)	57/87 (65.5)	37/107 (34.6)	3.59 (1.98–6.52)
Isolated gain(1q21)	24/37 (64.9)	15/47 (31.9)	3.94 (1.58–9.80)
Isolated amp(1q21)	14/17 (82.4)	9/23 (39.1)	7.26 (1.62–32.60)
1 revised HRCA	63/97 (64.9)	35/110 (31.8)	3.97 (2.23–7.08)
≥2 revised HRCAs	19/33 (57.6)	13/38 (34.2)	2.61 (1.00–6.83)



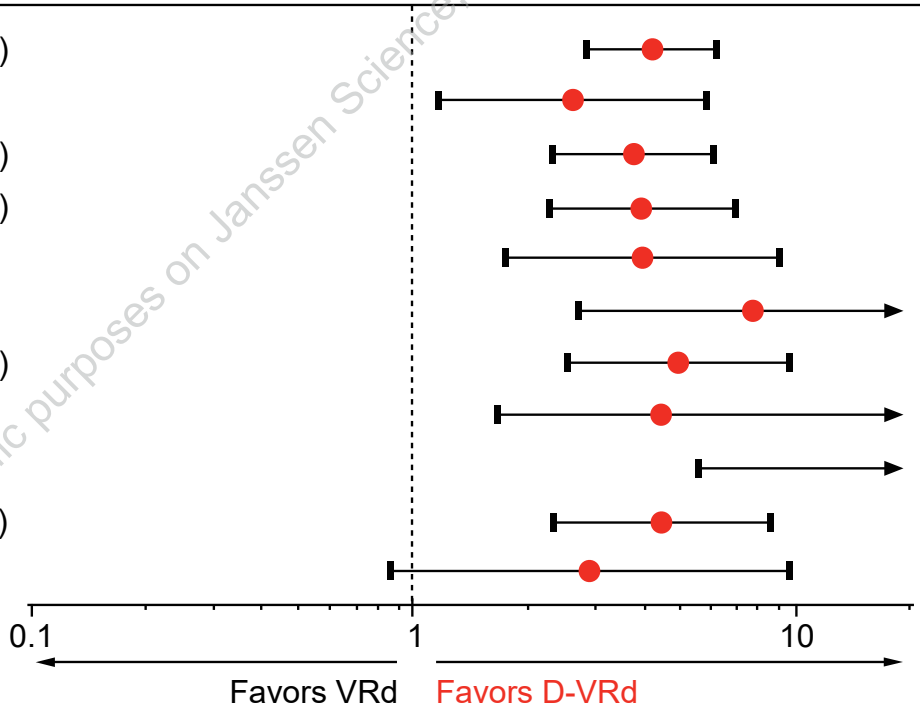
Subgroup analysis of MRD negativity (10^{-6}) based on cytogenetic risk status favored D-VRd followed by D-R maintenance

Presented by MA Dimopoulos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

PERSEUS: Subgroup Analysis of Sustained MRD Negativity (10^{-6}) Based on Cytogenetic Risk Status

Subgroup analysis of sustained MRD negativity (10^{-6}) for ≥12 months

	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)
Standard risk	137/264 (51.9)	54/266 (20.3)	4.24 (2.88–6.22)
High risk	23/76 (30.3)	11/78 (14.1)	2.64 (1.18–5.90)
Revised standard risk	87/174 (50.0)	35/167 (21.0)	3.77 (2.34–6.07)
Revised high risk	55/130 (42.3)	23/148 (15.5)	3.99 (2.27–7.01)
Gain(1q21)	25/59 (42.4)	11/71 (15.5)	4.01 (1.76–9.15)
Amp(1q21)	17/28 (60.7)	6/36 (16.7)	7.73 (2.42–24.63)
Gain(1q21) or amp(1q21)	42/87 (48.3)	17/107 (15.9)	4.94 (2.53–9.63)
Isolated gain(1q21)	19/37 (51.4)	9/47 (19.1)	4.46 (1.69–11.77)
Isolated amp(1q21)	13/17 (76.5)	3/23 (13.0)	21.67 (4.15–113.02)
1 revised HRCA	45/97 (46.4)	18/110 (16.4)	4.42 (2.32–8.42)
≥2 revised HRCAs	10/33 (30.3)	5/38 (13.2)	2.87 (0.87–9.51)

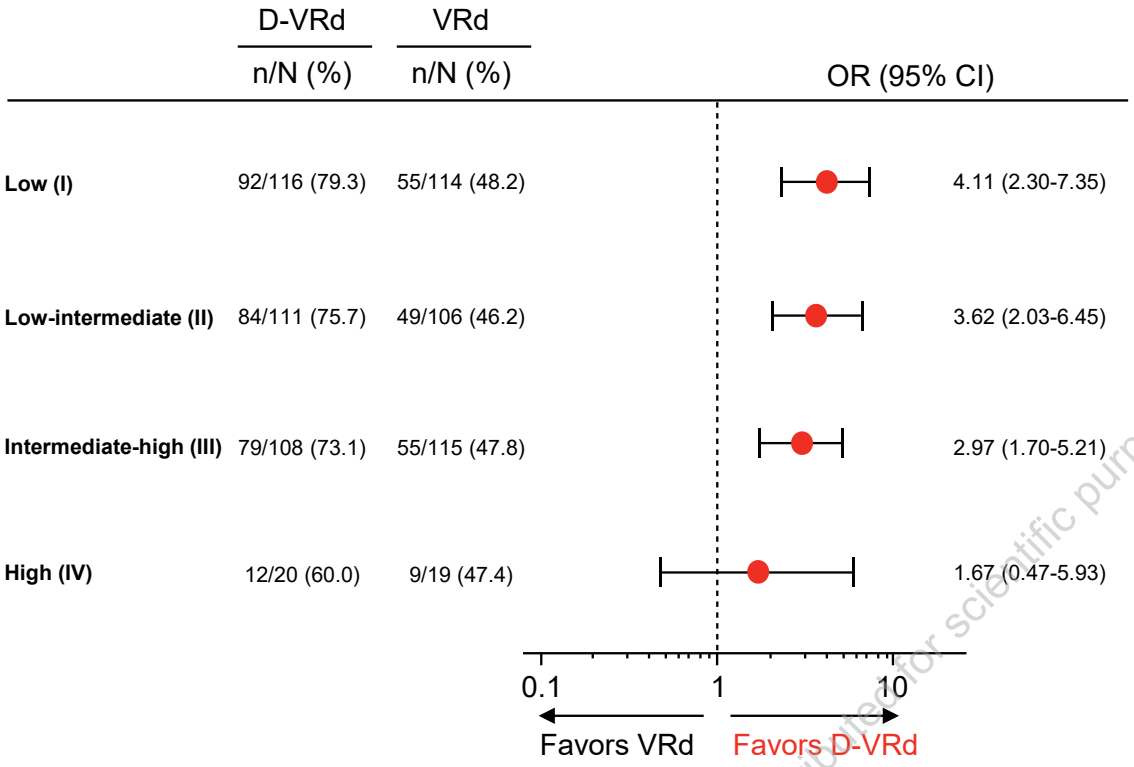


Subgroup analysis of sustained MRD negativity (10^{-6}) based on cytogenetic risk status favored D-VRd followed by D-R maintenance

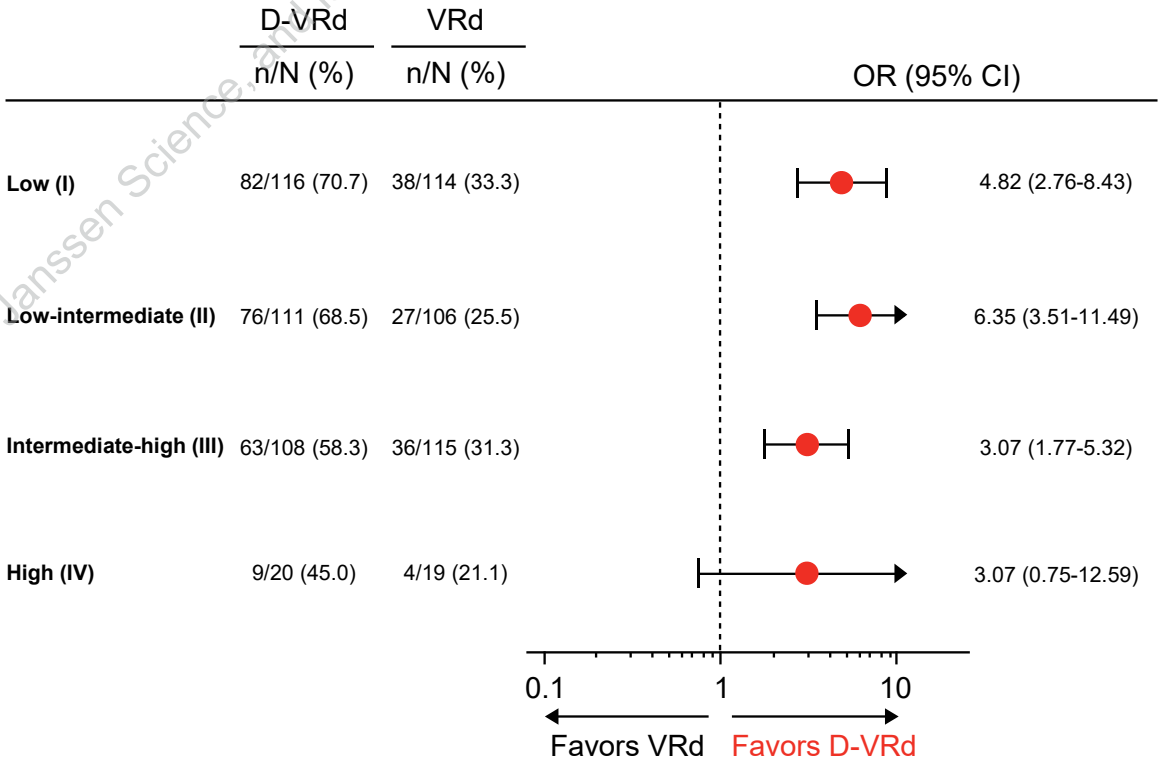
Presented by MA Dimopoulos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

PERSEUS: Subgroup Analyses of MRD Negativity (10^{-5}) Based on R2-ISS Disease Stage

Subgroup analysis of MRD negativity (10^{-5}) with ≥CR



Subgroup analysis of sustained MRD negativity (10^{-5}) for ≥12 months

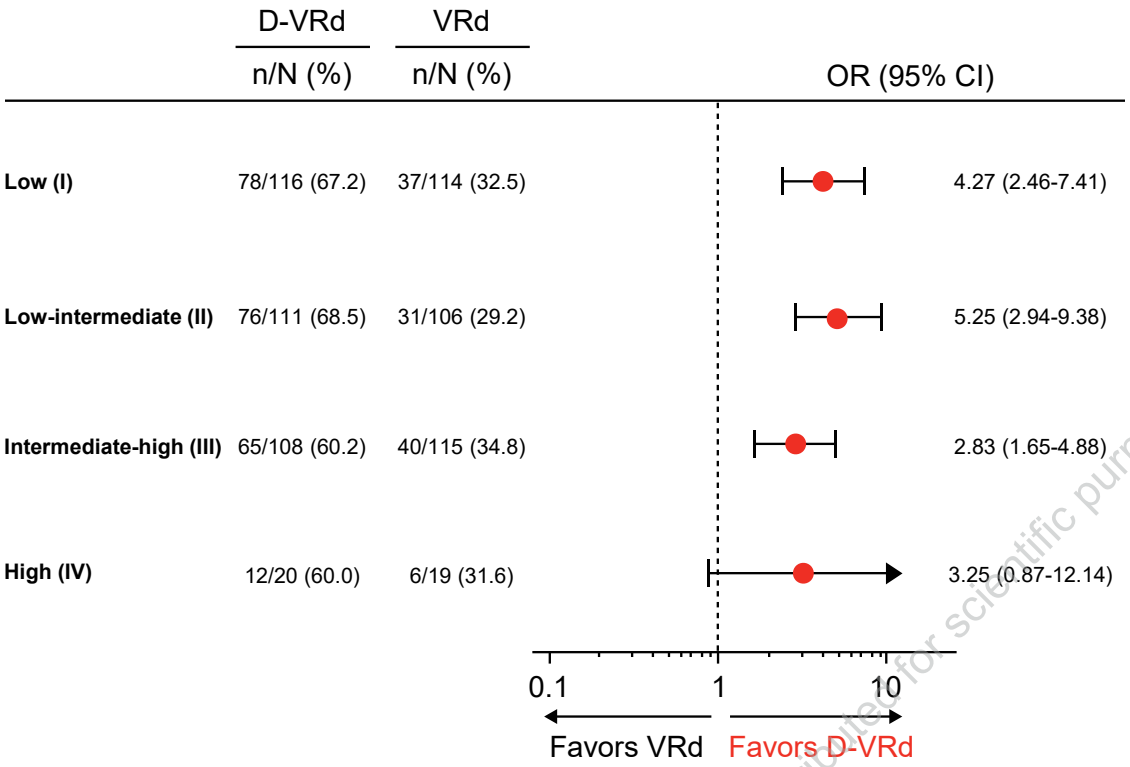


Subgroup analyses of MRD negativity (10^{-5}) based on R2-ISS disease stage favored D-VRd followed by D-R maintenance

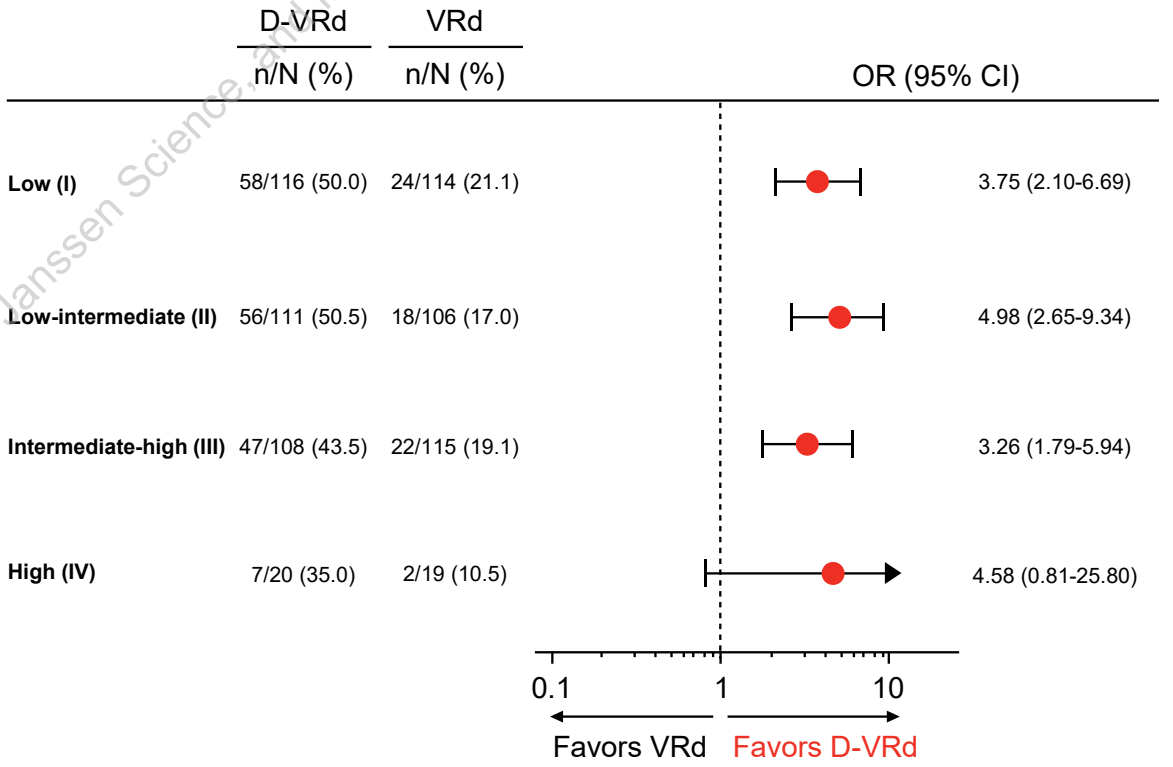
Presented by MA Dimopoulos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

PERSEUS: Subgroup Analyses of MRD Negativity (10^{-6}) Based on R2-ISS Disease Stage

Subgroup analysis of MRD negativity (10^{-6}) with ≥CR



Subgroup analysis of sustained MRD negativity (10^{-6}) for ≥12 months



Subgroup analyses of MRD negativity (10^{-6}) based on R2-ISS disease stage favored D-VRd followed by D-R maintenance

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PERSEUS: Conclusions

The addition of DARA SC to VRd induction/consolidation and R maintenance resulted in favorable PFS benefits and induced higher rates of deep and sustained MRD negativity:

- Regardless of R2-ISS disease stage
- Across all cytogenetic risk subgroups, including patients with revised high risk and patients with HRCAs such as gain(1q21) and amp(1q21)

The PERSEUS regimen demonstrates improved MRD negativity and PFS outcomes in patients with high-risk cytogenetics, including gain(1q21) or amp(1q21) and with ≥2 HRCAs

These results support the use of D-VRd induction/consolidation followed by D-R maintenance as a new standard of care for TE patients with NDMM, regardless of cytogenetic risk status

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- Data and safety monitoring committee
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EMN

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