High Risk MM

IMS Rio updates 2024

HR definitions

- ISS- JCO 2005
- RISS- JCO 2015 [del17p, T(4;14), T (14;16)]
- R2ISS- JCO 2022 [1q gain, no T(14;16)]
- IMS-IMWG:

  The HR subset should represent around 20% of NDMM

Summary of the IMS-IMWG 2024 Consensus HRMM Definition

Criteria for HRMM
Del(17p)[a] and/or TP53 mutation[b]
One of these translocations—t(4;14) or t(14;16) or t(14;20)—co-occurring with +1q and/or del(1p32)
Monoallelic del(1p32) along with +1q, or biallelic del(1p32)
High β2M (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL)

[a]CCF ≥20%, by analyses conducted on CD138-positive/purified cells.
[b]Assessed using an NGS-based method.
+1q, gain (3 copies) or amplification (≥4 copies) of the long arm of chromosome 1;
CCF, cancer clonal fraction; HRMM, high-risk multiple myeloma; NGS, next-generation sequencing.

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

*ClinicalTrials.gov Identifier: NCT03710603; sponsored by EMN in collaboration with Janssen Research & Development, LLC.

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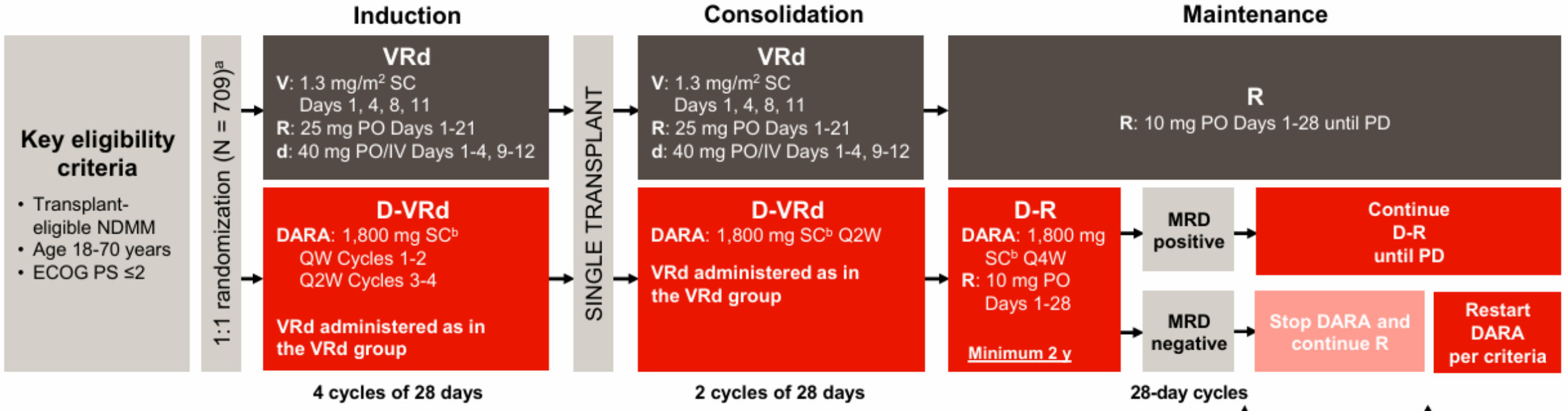
Presented by MA Dimopoulos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio De Janeiro, Brazil

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: 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.

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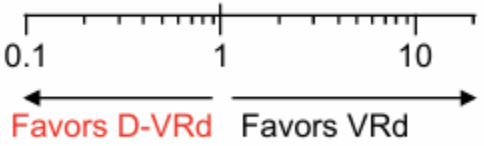
PERSEUS: Subgroup Analysis of PFS Based on Cytogenetic Risk Status (ITT)

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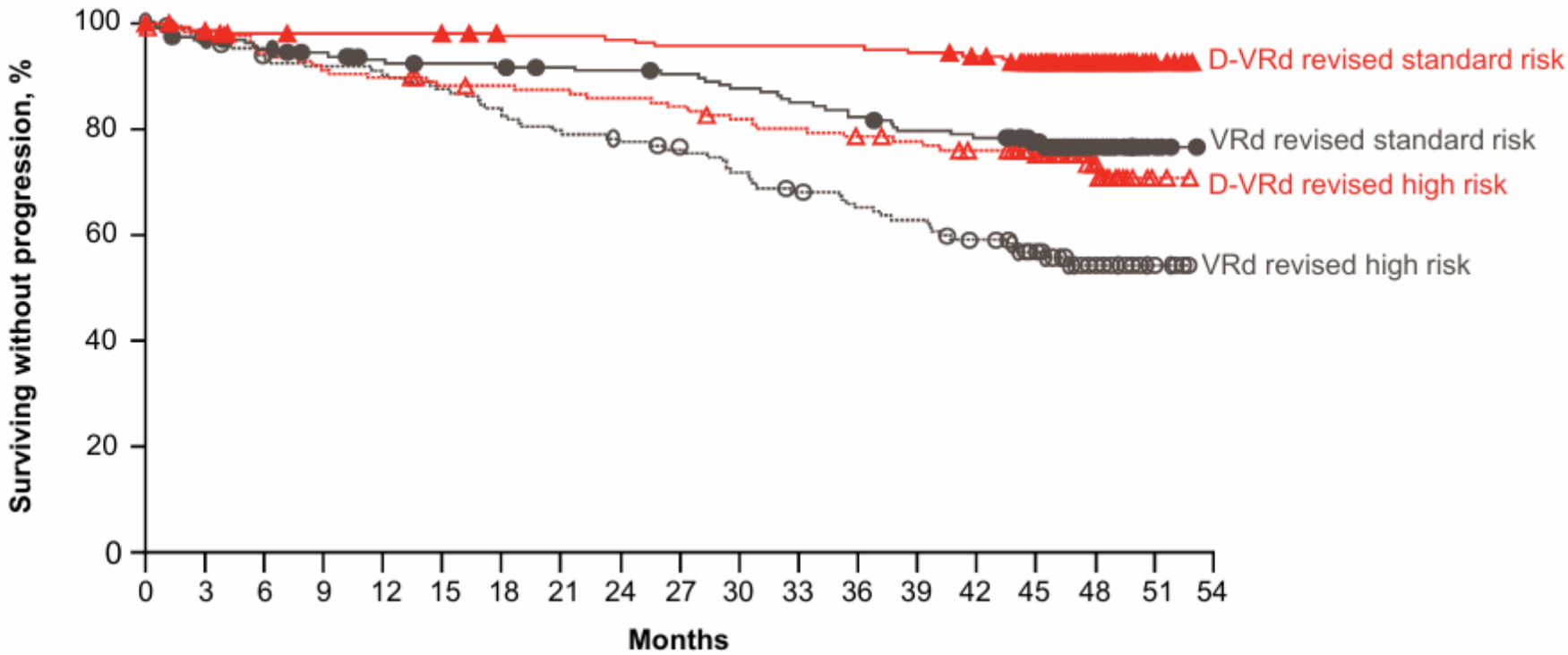
PERSEUS: Subgroup Analysis of PFS Based on Revised[a] Cytogenetic Risk Status (ITT)



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).

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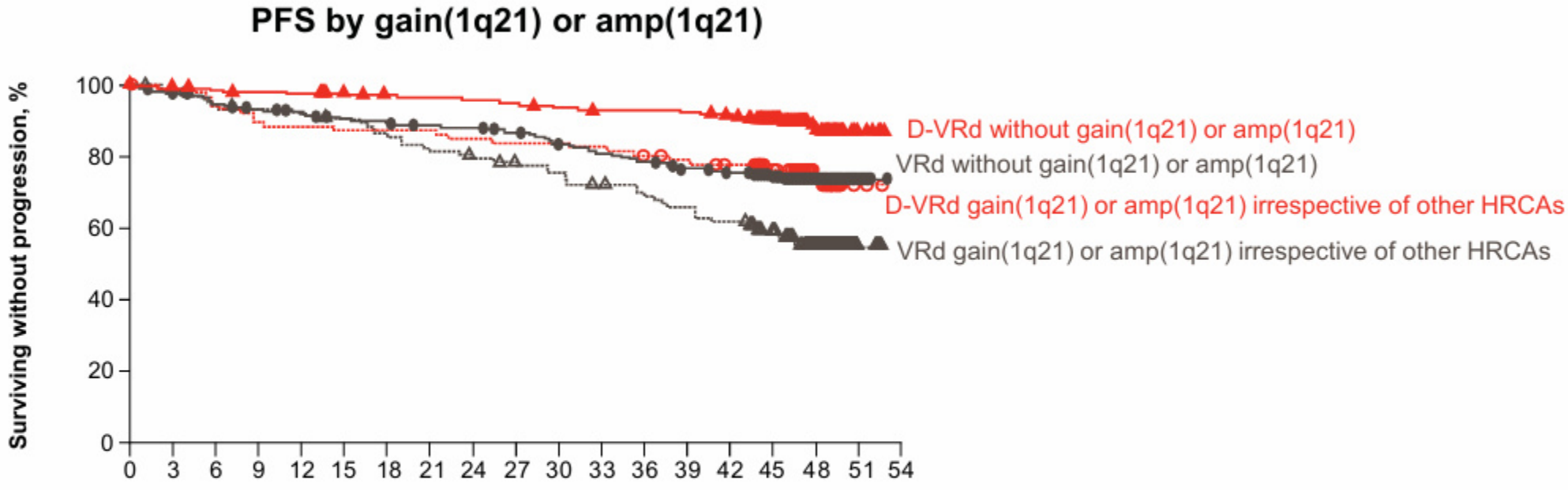
PERSEUS: Subgroup Analysis of PFS Based on Chromosome 1q21 Status



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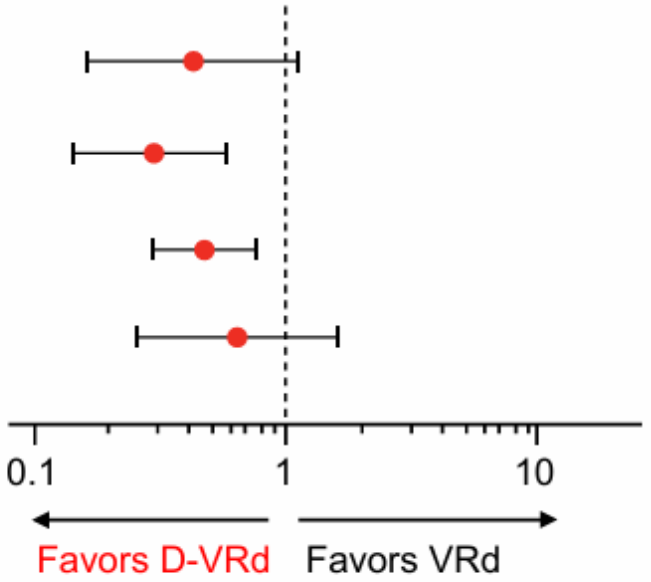
PERSEUS: Subgroup Analysis of PFS Based on R2-ISS Disease Stage

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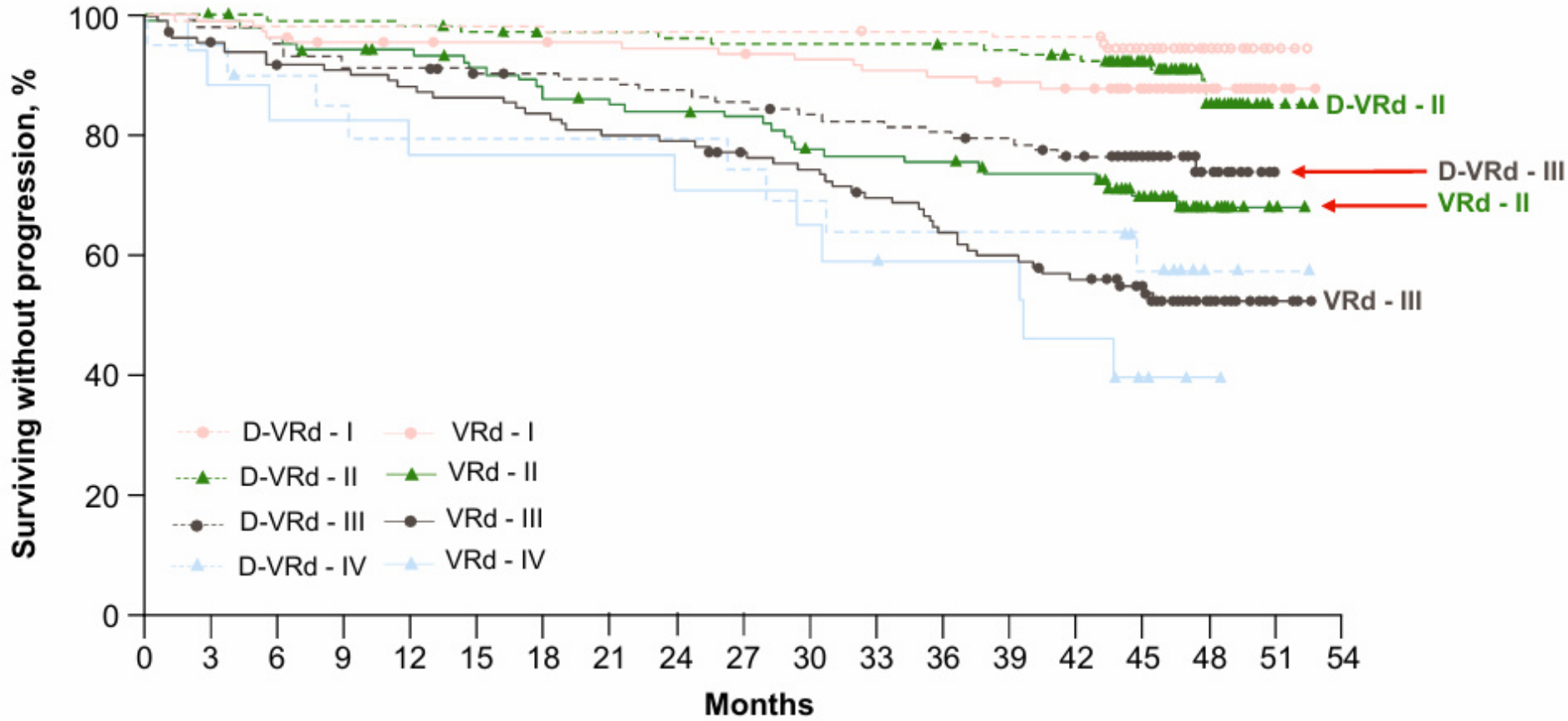
PERSEUS: Subgroup Analysis of PFS Based on R2-ISS Disease Stage (ITT)



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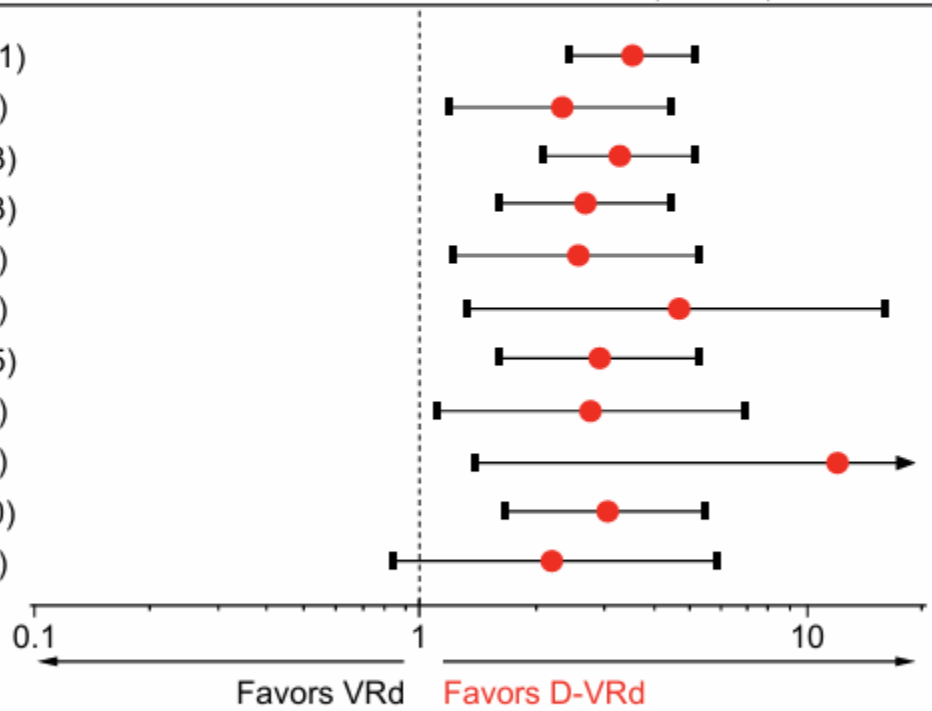
PERSEUS: Subgroup Analysis of MRD Negativity (10^{-5}) Based on Cytogenetic Risk Status

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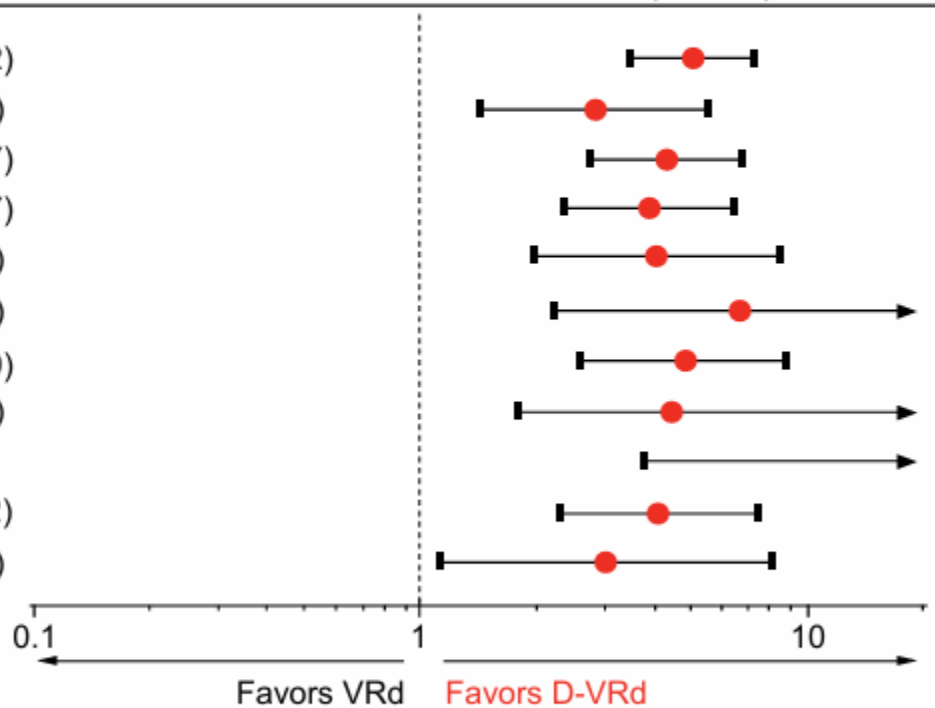
PERSEUS: Subgroup Analysis of Sustained MRD Negativity (10^{-5}) Based on Cytogenetic Risk Status

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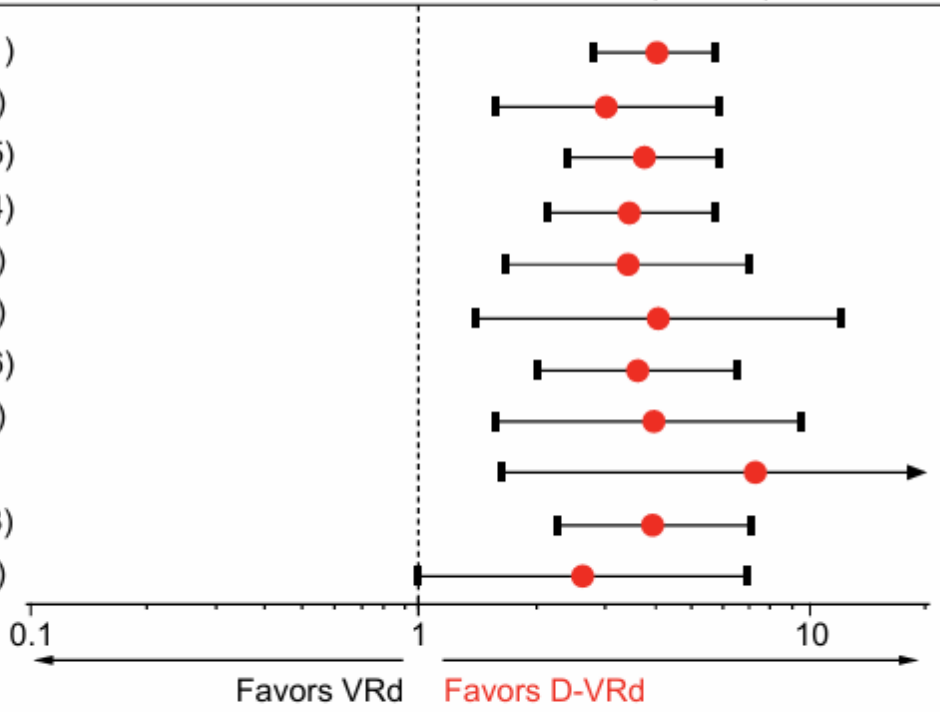
PERSEUS: Subgroup Analysis of MRD Negativity (10^{-6}) Based on Cytogenetic Risk Status

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

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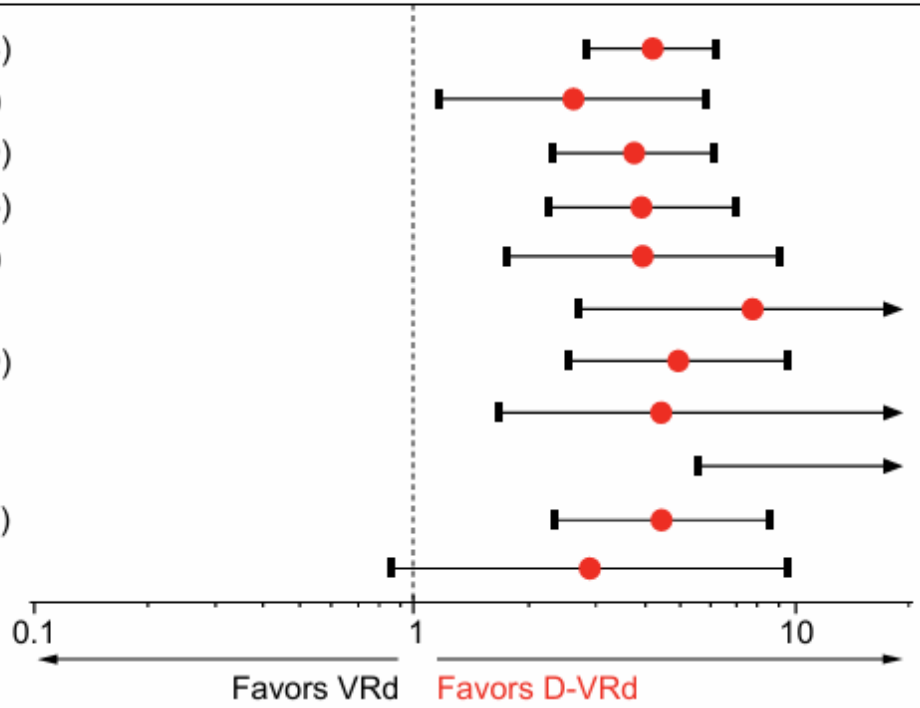
PERSEUS: Subgroup Analysis of Sustained MRD Negativity (10^{-6}) Based on Cytogenetic Risk Status

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

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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

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

The Importance of MRD Negativity in Managing High-Risk Myeloma

- CONCEPT Trial: Isa-KRDX6 induction therapy, followed by an ASCT, Isa-KRDX4 consolidation therapy, Isa-KR maintenance (2 years, then R maint). **82**% of patients achieved MRD negativity, and two-thirds of the patients lived longer than five years
- OPTIMUMM Trial: A UK study, Daratumumab, cyclophosphamide, Velcade, Revlimid, and dex X4 induction, followed by an ASCT. Consolidation with daratumumab, Velcade, Revlimid, and dex X18 , with DR maintenance. Here, **63**% of patients reached MRD negativity, and 84% of those were able to sustain it
- IFM 2018-04 Trial: A French study, DKRd X6 induction therapy, followed by an ASCT. DKRd X 4 consolidation, followed by a second ASCT and DR maintenance for 2 years. In this trial, **62**% of patients became MRD-negative

GMMG-CONCEPT trial

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Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma

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GMMG-CONCEPT trial

- An academic, investigator-initiated, multicenter, phase II trial enrolled patients with high-risk NDMM defined by ISS stage II/III combined with del17p, t(4;14), t(14;16), or more than three 1q21 copies as high-risk cytogenetic aberrations
- Patients received Isa-KRd inductionX6/consolidation and Isa-KR maintenance for 2 years
- TE patients received high-dose melphalan. TNE patients received two additional Isa KRd cycles postinduction
- The primary end point was MRD negativity (centrally assessed by NGS)

Results

- 153 pts (127 TE, 26 TNE) with a median age of 59 (TE) and 74 years (TNE)
- del17p and t(4;14) were the most common HR cytogenetic aberrations
- With a median follow-up of 54 months for TE pts, PFS-rates at 4, 5, and 6 years were 59%, 53%, and 53%, respectively
- Four-year-OS rate was 72%
- 5-Y- and 6-Y-OS-rates were 68% and 62%, respectively
- In TNE patients (mFU of 51 months), 4-Y- and 5-Y-PFS-rates were both 54% with 4-Y- and 5-Y-OS-rates of 69% each

Results

Achievement of MRD neg conferred significant benefit in PFS for TE pts (HR 0.34 [0.13;0.88]) which became even more pronounced for pts remaining in MRD-neg state (HR 0.11 [0.05;0.28])

Of 106 TE pts achieving MRD neg on study (84%), 85 pts had ≥1-Y-sustained MRD neg (80.2%)

For 18 TNE pts with MRD-negative results (69%), ≥1-Y-sustained MRD negativity was reported in 13 pts (72%)

Conclusions

An high potency of Isa-KRd to not only induce but also maintain MRD neg remissions in HR NDMM pts irrespective of transplant status

Six years after treatment initiation, more than half of these HR pts are still alive and progression-free

Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma

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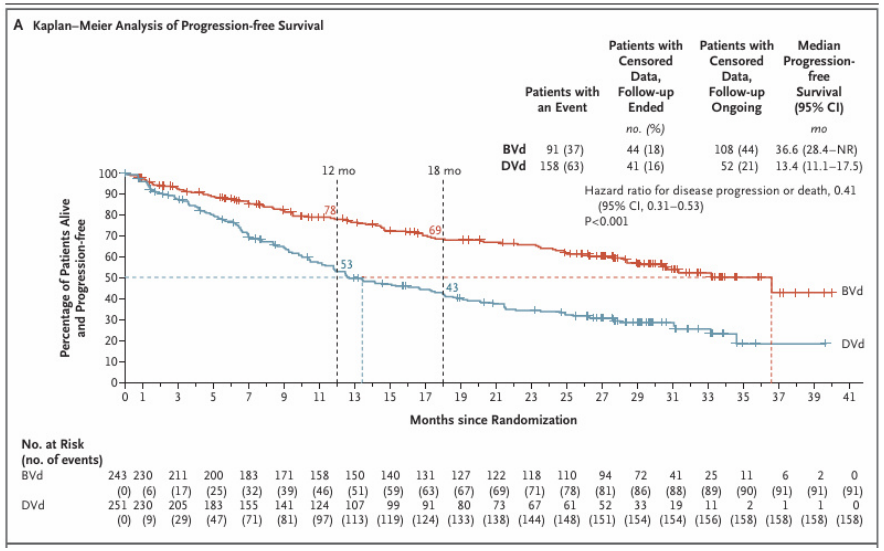
- Phase 3, open-label, randomized trial
- Belantamab, bortezomib, and dexamethasone (BVd), as compared with daratumumab, bortezomib, and dexamethasone (DVd), in patients who had progression of MM **after at least one line** of therapy
- The primary endpoint was PFS. Key secondary endpoints were overall survival, response duration, and minimal residual disease (MRD)–negative status

Previous immunomodulatory drugs — no. (%)		
Any	198 (81)	216 (86)
Lenalidomide	127 (52)	130 (52)
Thalidomide	121 (50)	144 (57)
Pomalidomide	25 (10)	19 (8)

DREAMM- 7- Results

- 494 patients were randomly assigned to receive BVd (243 patients) or DVd (251 patients)
- At a median follow-up of 28.2 months (range, 0.1 to 40.0), **median PFS was 36.6 months** (95% CI, 28.4 to not reached) in the BVd group and **13.4 months** (95% CI, 11.1 to 17.5) in the DVd group (HR 0.41; 95% CI, 0.31 to 0.53; P<0.001)
- OSat 18 months was 84% in the BVd group and 73% in the DVd group- not mature



Issues for discussion

Bela +Vd vs DVd demonstrated PFS of 36.6 vs 13 m -> i.e 23 m improvement in PFS, so the efficacy seems very impressive. However, this was a **Dara naïve** patient population, and Dara is currently used as first-line, so the trial population is not reflective of a real-world 2L patient population. Moreover, **only a third are len refractory**

Maybe Dara comparator arm underperformed? Bortezomib was discontinued after 9 cycles. However, EMD was 5% in the Bela arm and 10% in the Dara arm

Grade 3 or higher ocular adverse events occurred in 34% of patients receiving Bela, while **9% stopped treatment due to these side effects**. A total of 79% of Bela patients had all-grade ocular AEs. **98% resolved and the median time to resolution was 22d**

ORIGINAL ARTICLE

Belantamab Mafodotin, Pomalidomide, and Dexamethasone in Multiple Myeloma

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- Phase 3, randomized, open-label trial, that evaluated belantamab, pomalidomide, and dexamethasone (BPd), as compared with pomalidomide, bortezomib, and dexamethasone (PVd), in lenalidomide-exposed patients who had relapsed or refractory myeloma after **at least one line of therapy**
- The primary endpoint was PFS

Refractory status according to agent — no. (%)‖		
Proteasome inhibitor	40 (26)	35 (24)
Bortezomib	16 (10)	8 (5)
Carfilzomib	18 (12)	23 (16)
Ixazomib	8 (5)	11 (7)
Immunomodulatory drugs	127 (82)	111 (76)
Lenalidomide	125 (81)	111 (76)
Thalidomide	9 (6)	6 (4)
Anti-CD38 antibodies	35 (23)	36 (24)
Daratumumab	33 (21)	34 (23)
Isatuximab	2 (1)	2 (1)
CD38 inhibitors	0	1 (1)
Chemotherapy	15 (10)	11 (7)
Glucocorticoids	74 (48)	62 (42)

DREAMM-8 - Results

- 302 patients underwent randomization; 155 were assigned to the BPd group, and 147 to the PVd group.
- At a median follow-up of 21.8 months the 12-month estimated PFS with BPd was 71% as compared with 51% with PVd (hazard ratio for disease progression or death, 0.52; 95% CI, 0.37 to 0.73; P<0.001)
- Data on overall survival were immature