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

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Key Takeaway

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

Conclusions

The addition of DARA SC to VRd induction/consolidation and R maintenance resulted in favorable PFS benefits across all cytogenetic risk subgroups, including those with revised high risk and the presence of gain(1q21) or amp(1q21), versus VRd followed by R maintenance

D-VRd followed by D-R maintenance induced higher rates of deep and sustained MRD negativity versus VRd followed by R across all cytogenetic risk subgroups

Results from this expanded subgroup analysis of PERSEUS based on the presence of HRCAs, including gain(1q21) and amp(1q21), support the addition of DARA SC to VRd therapy during both induction/consolidation and maintenance in this patient population

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Disclosure

MAD serves as a consultant for Amgen, BeiGene, Bristol Myers Squibb, Celgene Corporation, GSK, Janssen, Menarini Silicon Biosystems, Regeneron Pharmaceuticals, Sanofi, and Takeda.

Introduction

- Daratumumab (DARA) is a human IgG$_\kappa$ monoclonal antibody targeting CD38 with a direct on-tumor[1-4] and immunomodulatory[5-7] mechanism of action, demonstrating greater cytotoxicity toward multiple myeloma cells ex vivo compared with analogs of other CD38 antibodies[8]
  - DARA is approved in combination with other standard-of-care regimens for patients with newly diagnosed multiple myeloma (NDMM)[9,10] and has been used to treat >518,000 patients worldwide[11]
  - DARA has consistently demonstrated clinical efficacy in patients with NDMM and relapsed/refractory multiple myeloma in several pivotal clinical trials[12-15]
- Despite the advancements in antimyeloma treatments, patients with high-risk cytogenetic abnormalities (HRCAs) often have a poor prognosis and experience poor disease outcomes[16]
- In the primary analysis of the phase 3 PERSEUS study (ClinicalTrials.gov Identifier: NCT03710603), with a median follow-up of 47.5 months, subcutaneous DARA (DARA SC) plus bortezomib, lenalidomide, and dexamethasone (D-VRd) followed by D-R maintenance significantly improved progression-free survival (PFS) and increased depth of response, including complete response or better (≥CR) and minimal residual disease (MRD)–negativity rates, versus VRd followed by R maintenance alone in transplant-eligible (TE) patients with NDMM[17]
  - Overall and sustained MRD-negativity rates (10^{-5} and 10^{-6}) were significantly higher with D-VRd followed by D-R maintenance versus VRd followed by R maintenance[17,18]
    - Overall (10^{-5}): 75.2% versus 47.5% (P <0.0001)
    - Overall (10^{-6}): 65.1% versus 32.2% (P <0.0001)
    - Sustained (≥12 months; 10^{-5}): 64.8% versus 29.7% (P <0.0001)
    - Sustained (≥12 months; 10^{-6}): 47.3% versus 18.6% (P <0.0001)
  - Furthermore, consistent benefits in terms of PFS, ≥CR rates, and MRD-negativity rates were observed across clinically relevant subgroups, including patients with high cytogenetic risk (ie, del[17p], t[4;14], or t[14;16])
- Here, we report an expanded analysis of PERSEUS clinical outcomes (PFS, overall MRD negativity, and sustained MRD negativity) based on the presence of HRCAs, including gain(1q21) and amp(1q21)

Methods

Study design

- Patients aged 18 to 70 years with NDMM who were eligible for high-dose chemotherapy and autologous stem cell transplant (ASCT) were randomized 1:1 to receive D-VRd followed by D-R maintenance or VRd followed by R maintenance
  - Patients in both arms received up to six 28-day cycles (4 pre–ASCT induction; 2 post–ASCT consolidation) of VRd (V: 1.3 mg/m^2 SC on Days 1, 4, 8, and 11; R: 25 mg orally once daily on Days 1-21; d: 40 mg orally/intravenously on Days 1-4 and 9-12) followed by R maintenance (10 mg orally once daily on Days 1-28)
  - Patients in the D-VRd/D-R arm also received DARA SC (DARA 1,800 mg + recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; Halozyme]) QW in Cycles 1 to 2, Q2W in Cycles 3 to 6, and Q4W during maintenance until progressive disease or unacceptable toxicity

Patient subgroups

- The following cytogenetic risk subgroups were explored in this analysis:
  - Standard risk (per protocol), defined as none of the following HRCAs: del(17p), t(4;14), t(14;16)
  - High risk (per protocol), defined as 1 or more of the following HRCAs: del(17p), t(4;14), t(14;16)
  - Revised standard risk, defined as none of the following HRCAs: del(17p), t(4;14), t(14;16), gain(1q21), amp(1q21)
  - Revised high risk, defined as 1 or more of the following HRCAs: del(17p), t(4;14), t(14;16), gain(1q21), amp(1q21)
  - Gain(1q21), defined as the presence of 3 copies of chromosome 1q21, with or without other HRCAs
  - Amp(1q21), defined as the presence of 4 or more copies of chromosome 1q21, with or without other HRCAs
  - Gain(1q21) or amp(1q21), defined as the presence of gain(1q21) or amp(1q21), with or without other HRCAs
  - Isolated gain(1q21), defined as the presence of 3 copies of chromosome 1q21, without any other HRCAs
  - Isolated amp(1q21), defined as the presence of 4 or more copies of chromosome 1q21, without any other HRCAs
  - 1 revised HRCA, defined as the presence of only 1 revised HRCA
  - ≥2 revised HRCAs, defined as the presence of 2 or more revised HRCAs
- Cytogenetic risk was centrally assessed by fluorescence in situ hybridization
  - Patients were considered positive for a chromosome abnormality when the test result met or exceeded the threshold established by the central laboratory

Assessments

- PFS (primary endpoint) was defined as the time from the date of randomization to the date of first disease progression (as per International Myeloma Working Group response criteria)[19] or death, whichever occurred first
  - PFS was compared between treatment groups using a log-rank test, and the Kaplan–Meier method was used to estimate PFS distributions
  - Treatment effect (hazard ratio [HR]) and corresponding 95% confidence intervals (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 (odds ratio) and corresponding 95% CIs were estimated using a Mantel–Haenszel estimation

Results

Patients

- In total, 709 patients were randomized (D-VRd, n = 355; VRd, n = 354)
  - Patient demographic and baseline characteristics were well balanced between groups[17] (**Table 1**)

Table 1: Demographic and baseline characteristics of the ITT population[a]

Characteristic	D-VRd (n = 355)	VRd (n = 354)
Age		
Median (range), years	61.0 (32-70)	59.0 (31-70)
Male, n (%)	211 (59.4)	205 (57.9)
Race, n (%)		
Asian	4 (1.1)	6 (1.7)
Black	5 (1.4)	4 (1.1)
White	330 (93.0)	323 (91.2)
Other	4 (1.1)	3 (0.8)
Not reported	12 (3.4)	18 (5.1)
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 risk,[b] n (%)		
Standard risk	264 (74.4)	266 (75.1)
High risk	76 (21.4)	78 (22.0)
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)
Indeterminate	15 (4.2)	10 (2.8)
Revised cytogenetic risk,[c] n (%)		
Revised standard risk	174 (49.0)	167 (47.2)
Revised high risk	130 (36.6)	148 (41.8)
Indeterminate	51 (14.4)	39 (11.0)

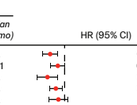
ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; ISS, International Staging System; FISH, fluorescence in situ hybridization.
[a]The ITT population included all randomized patients.
[b]Cytogenetic risk was based on FISH; high risk was defined as the presence of del(17p), t(4;14), or t(14;16).
[c]Revised cytogenetic risk was defined as the presence of del(17p), t(4;14), t(14;16), gain(1q21), or amp(1q21).

Progression-free survival

- After a median follow-up of 47.5 months, PFS favored D-VRd followed by D-R maintenance versus VRd followed by R maintenance across all cytogenetic risk subgroups (**Figure 1**)
  - HR point estimates for PFS favored D-VRd versus VRd for revised standard (HR, 0.29; 95% CI, 0.15-0.56; P = 0.0001) and revised high cytogenetic risk (HR, 0.53; 95% CI, 0.35-0.81; P = 0.0027; **Figure 2**)
  - HR point estimates for PFS also favored D-VRd versus VRd in patients with the presence of gain(1q21), amp(1q21), and gain(1q21) or amp(1q21), irrespective of other HRCAs (**Figure 3**)

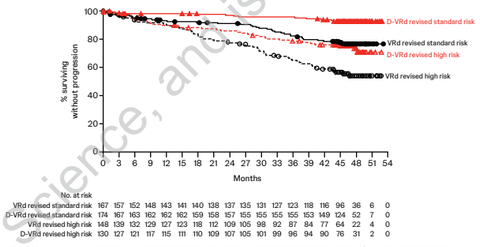
Figure 1: Cytogenetic risk subgroup analysis of PFS (ITT)

	D-VRd n/N	D-VRd Median PFS (mo)	VRd n/N	VRd 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, progression-free survival; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; NE, not estimable; HRCA, high-risk cytogenetic abnormality.

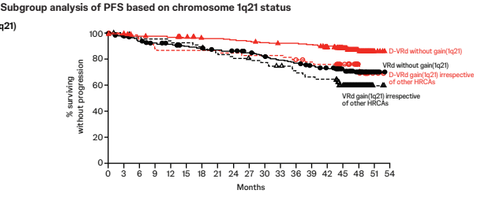
Figure 2: Subgroup analysis of PFS based on revised[a] cytogenetic risk status (ITT)



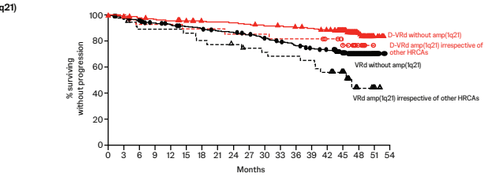
PFS, progression-free survival; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HRCA, high-risk cytogenetic abnormality.
[a]Revised high risk, defined as the presence of 1 or more of the following HRCAs: del(17p), t(4;14), t(14;16), gain(1q21), amp(1q21).

Figure 3: Subgroup analysis of PFS based on chromosome 1q21 status

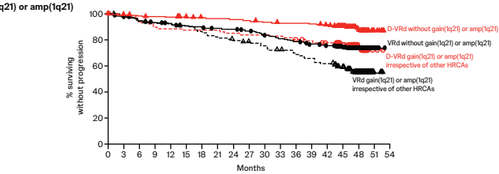
A. Gain(1q21)



B. Amp(1q21)



C. Gain(1q21) or amp(1q21)



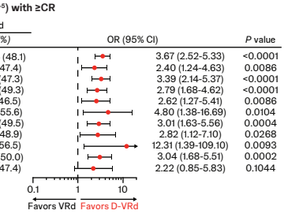
PFS, progression-free survival; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HRCA, high-risk cytogenetic abnormality.

Minimal residual disease

- Subgroup analysis of overall and sustained (≥12 months) MRD negativity (at 10^{-5} and 10^{-6}) with ≥CR rates based on cytogenetic risk markers favored treatment with D-VRd followed by D-R maintenance over VRd followed by R maintenance, regardless of high-risk cytogenetic markers (**Figures 4-7**)

Figure 4: Subgroup analysis of MRD negativity (10^{-5}) with ≥CR

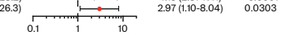
	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)	P value
Standard risk	204/264 (77.3)	128/266 (48.1)	3.67 (2.52-5.33)	<0.0001
High risk	52/76 (68.4)	37/78 (47.4)	2.40 (1.24-4.63)	0.0086
Revised standard risk	131/174 (75.3)	79/167 (47.3)	3.39 (2.14-5.37)	<0.0001
Revised high risk	95/130 (73.1)	73/148 (49.3)	2.79 (1.68-4.62)	<0.0001
Gain(1q21)	41/59 (69.5)	33/71 (46.5)	2.62 (1.27-5.41)	0.0086
Amp(1q21)	24/28 (85.7)	20/36 (55.6)	4.80 (1.38-16.69)	0.0104
Gain(1q21) or amp(1q21)	65/87 (74.7)	53/107 (49.5)	3.01 (1.63-5.56)	0.0004
Isolated gain(1q21)	27/37 (73.0)	23/47 (48.9)	2.82 (1.12-7.10)	0.0268
Isolated amp(1q21)	16/17 (94.1)	13/23 (56.5)	12.31 (1.39-109.10)	0.0093
1 revised HRCA	73/97 (75.3)	55/110 (50.0)	3.04 (1.68-5.51)	0.0002
≥2 revised HRCAs	22/33 (66.7)	18/38 (47.4)	2.22 (0.85-5.83)	0.1044



MRD, minimal residual disease; CR, complete response; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; OR, odds ratio; CI, confidence interval; HRCA, high-risk cytogenetic abnormality.

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

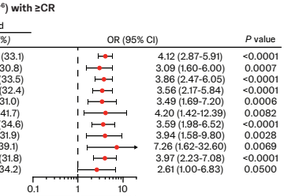
	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)	P value
Standard risk	183/264 (69.3)	83/266 (31.2)	4.98 (3.45-7.20)	<0.0001
High risk	37/76 (48.7)	20/78 (25.6)	2.75 (1.40-5.42)	0.0032
Revised standard risk	115/174 (66.1)	53/167 (31.7)	4.19 (2.67-6.59)	<0.0001
Revised high risk	77/130 (59.2)	41/148 (27.7)	3.79 (2.30-6.26)	<0.0001
Gain(1q21)	37/59 (62.7)	21/71 (29.6)	4.00 (1.92-8.34)	0.0002
Amp(1q21)	20/28 (71.4)	10/36 (27.8)	6.50 (2.17-19.48)	0.0006
Gain(1q21) or amp(1q21)	57/87 (65.5)	31/107 (29.0)	4.66 (2.54-8.56)	<0.0001
Isolated gain(1q21)	25/37 (67.6)	15/47 (31.9)	4.44 (1.77-11.17)	0.0012
Isolated amp(1q21)	15/17 (88.2)	6/23 (26.1)	21.25 (3.71-121.61)	0.0001
1 revised HRCA	60/97 (61.9)	31/110 (28.2)	4.13 (2.31-7.41)	<0.0001
≥2 revised HRCAs	17/33 (51.5)	10/38 (26.3)	2.97 (1.10-8.04)	0.0303



MRD, minimal residual disease; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; OR, odds ratio; CI, confidence interval; HRCA, high-risk cytogenetic abnormality.

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

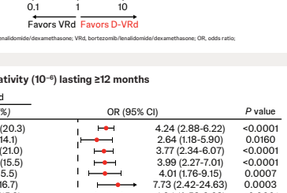
	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)	P value
Standard risk	177/264 (67.0)	88/266 (33.1)	4.12 (2.87-5.91)	<0.0001
High risk	44/76 (57.9)	24/78 (30.8)	3.09 (1.60-6.00)	0.0007
Revised standard risk	115/174 (66.1)	56/167 (33.5)	3.86 (2.47-6.05)	<0.0001
Revised high risk	82/130 (63.1)	48/148 (32.4)	3.56 (2.17-5.84)	<0.0001
Gain(1q21)	36/59 (61.0)	22/71 (31.0)	3.49 (1.69-7.20)	0.0006
Amp(1q21)	21/28 (75.0)	15/36 (41.7)	4.20 (1.42-12.39)	0.0082
Gain(1q21) or amp(1q21)	57/87 (65.5)	37/107 (34.6)	3.59 (1.98-6.52)	<0.0001
Isolated gain(1q21)	24/37 (64.9)	15/47 (31.9)	3.94 (1.58-9.80)	0.0028
Isolated amp(1q21)	14/17 (82.4)	9/23 (39.1)	7.26 (1.62-32.60)	0.0069
1 revised HRCA	63/97 (64.9)	35/110 (31.8)	3.97 (2.23-7.08)	<0.0001
≥2 revised HRCAs	19/33 (57.6)	13/38 (34.2)	2.61 (1.00-6.83)	0.0500



MRD, minimal residual disease; CR, complete response; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; OR, odds ratio; CI, confidence interval; HRCA, high-risk cytogenetic abnormality.

Figure 7: Subgroup analysis of sustained MRD negativity (10^{-6}) lasting ≥12 months

	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)	P value
Standard risk	137/264 (51.9)	54/266 (20.3)	4.24 (2.88-6.22)	<0.0001
High risk	23/76 (30.3)	11/78 (14.1)	2.64 (1.18-5.90)	0.0160
Revised standard risk	87/174 (50.0)	35/167 (21.0)	3.77 (2.34-6.07)	<0.0001
Revised high risk	55/130 (42.3)	23/148 (15.5)	3.99 (2.27-7.01)	<0.0001
Gain(1q21)	25/59 (42.4)	11/71 (15.5)	4.01 (1.76-9.15)	0.0007
Amp(1q21)	17/28 (60.7)	6/36 (16.7)	7.73 (2.42-24.63)	0.0003
Gain(1q21) or amp(1q21)	42/87 (48.3)	17/107 (15.9)	4.94 (2.53-9.63)	<0.0001
Isolated gain(1q21)	19/37 (51.4)	9/47 (19.1)	4.46 (1.69-11.77)	0.0020
Isolated amp(1q21)	13/17 (76.5)	3/23 (13.0)	21.67 (4.15-113.02)	<0.0001
1 revised HRCA	45/97 (46.4)	18/110 (16.4)	4.42 (2.32-8.42)	<0.0001
≥2 revised HRCAs	10/33 (30.3)	5/38 (13.2)	2.87 (0.87-9.51)	0.0797



MRD, minimal residual disease; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; OR, odds ratio; CI, confidence interval; HRCA, high-risk cytogenetic abnormality.

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