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Daratumumab + Bortezomib, Lenalidomide, and Dexamethasone (D-VRd) Versus VRd in Transplant-Ineligible/Transplant-Deferred Newly Diagnosed Multiple Myeloma: Phase 3 CEPHEUS Trial Cytogenetic Subgroup Analysis

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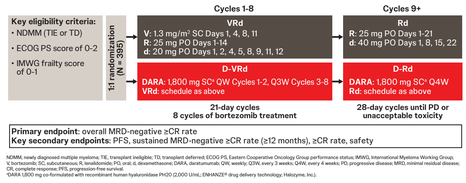
Introduction

- High-risk cytogenetic abnormalities (HRCAs) are associated with poor survival outcomes in patients with multiple myeloma[1]
- The phase 3 CEPHEUS trial in patients with transplant-ineligible (TIE) or transplant-deferred (TD) newly diagnosed multiple myeloma (NDMM) showed that the addition of daratumumab subcutaneous (SC) to bortezomib, lenalidomide, and dexamethasone (VRd)[2]:
  - Significantly improved rates of overall and sustained minimal residual disease (MRD) negativity with complete response or better (≥CR) in the intent-to-treat (ITT) population
  - Significantly improved progression-free survival (PFS) in the ITT population (hazard ratio [HR], 0.57; $P = 0.0005$)
  - Had a safety profile consistent with each individual drug's profile
- Daratumumab previously showed benefit in patients with NDMM with HRCAs, including gain (3 copies) or amplification (amp; ≥4 copies) of chromosome 1q21 (1q)[3-5]
- In this post hoc analysis, we report outcomes in cytogenetic risk subgroups in CEPHEUS

Methods

- CEPHEUS is a randomized, open-label, multicenter, phase 3 trial (**Figure 1**)
- Bone marrow MRD was assessed by next-generation sequencing (clonoSEQ®; Adaptive Biotechnologies)
  - Overall MRD-negativity rate was defined as the proportion of patients who achieved both ≥CR and MRD-negative status; sustained MRD negativity was defined in patients with ≥CR as MRD negativity at 2 assessments without any MRD positivity in between
- Fluorescence in situ hybridization was used to detect the following HRCAs: del(17p), t(4;14), t(14;16), and gain(1q) or amp(1q)
- Protocol-defined HRCAs were del(17p), t(4;14), and t(14;16); revised HRCAs were del(17p), t(4;14), t(14;16), and gain/amp(1q)
  - Patients with standard cytogenetic risk, per protocol, were negative for all protocol-defined HRCAs; those with revised standard cytogenetic risk were negative for all revised HRCAs
  - Patients with high cytogenetic risk, per protocol, were positive for any protocol-defined HRCA; those with revised high cytogenetic risk were positive for any revised HRCA
- Additional cytogenetic risk subgroups assessed were those with gain(1q), amp(1q), 1 revised HRCA, ≥2 revised HRCAs, isolated gain(1q), isolated amp(1q), isolated gain/amp(1q), and gain/amp(1q) plus ≥1 HRCA

Figure 1: Study design



NDMM, newly diagnosed multiple myeloma; TIE, transplant ineligible; TD, transplant deferred; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; V, bortezomib; SC, subcutaneous; R, lenalidomide; PO, oral; d, dexamethasone; DARA, daratumumab; QW, weekly; Q3W, every 3 weeks; Q4W, every 4 weeks; PD, progressive disease; MRD, minimal residual disease; CR, complete response; PFS, progression-free survival.
*DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 (2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc.).

Results

Study population

- 395 patients were randomized 1:1 to receive daratumumab plus bortezomib, lenalidomide, and dexamethasone (D-VRd; n = 197) or VRd (n = 198)
- HRCAs were generally balanced between treatment arms (**Table 1**)
  - Other baseline characteristics, which were previously described,[2] were also well balanced
- At a median of 58.7 months of follow-up, median treatment duration was 59.0 cycles with D-VRd versus 37.0 cycles with VRd

Table 1: Baseline cytogenetic risk[a]

Characteristic, n (%)	D-VRd (n = 197)	VRd (n = 198)
Protocol-defined standard risk	149 (75.6)	149 (75.3)
Protocol-defined high risk	25 (12.7)	27 (13.6)
Revised standard risk	94 (47.7)	90 (45.5)
Revised high risk	83 (42.1)	84 (42.4)
Gain(1q)	43 (21.8)	48 (24.2)
Amp(1q)	31 (15.7)	20 (10.1)
1 revised HRCA	66 (33.5)	72 (36.4)
≥2 revised HRCAs	17 (8.6)	12 (6.1)
Isolated gain(1q)	35 (17.8)	40 (20.2)
Isolated amp(1q)	23 (11.7)	17 (8.6)
Isolated gain/amp(1q)	58 (29.4)	57 (28.8)
Gain/amp(1q) plus ≥1 HRCA	16 (8.1)	11 (5.6)

D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; amp, amplification; HRCA, high-risk cytogenetic abnormality.
[a]New cytogenetic-risk criteria not available at time of analyses.

Overall and sustained MRD-negative ≥CR rates

- Overall and sustained (≥12- and ≥24-month) MRD-negative ≥CR rates at 10^{-6} were higher with D-VRd versus VRd in standard cytogenetic risk subgroups (**Figure 2**)
- In subgroups with HRCAs, at 10^{-5}, D-VRd versus VRd led to generally favorable treatment effects for D-VRd for overall MRD-negative ≥CR rate (**Figure 2A**) and sustained (≥12- and ≥24-month) MRD-negative ≥CR rate (**Figure 2B** and **Figure 2C**), with some exceptions; in the protocol-defined high-risk subgroup:
  - This, and an unexpectedly high overall MRD-negative ≥CR rate with VRd, was potentially due to small sample sizes (**Figure 2A**); furthermore, due to a shorter median treatment duration in the D-VRd arm (27.0 vs 35.5 cycles, respectively), there was a higher rate of missing post-baseline samples (24.0% vs 14.8%); therefore, patients in the D-VRd arm had fewer opportunities to achieve or be tested for MRD negativity
- Results at 10^{-6} were similar to those at 10^{-5} except (**Figure 3**):
  - Higher overall MRD-negative ≥CR rates with D-VRd versus VRd in the 1 revised HRCA, isolated amp(1q), and isolated gain/amp(1q) subgroups (**Figure 3A**)
  - Higher ≥12-month sustained MRD-negative ≥CR rates at 10^{-6} with D-VRd versus VRd in the isolated gain/amp(1q) subgroup (**Figure 3B**)

Figure 2: Overall and sustained MRD-negative (10^{-5}) ≥CR rates

A. Overall MRD negativity

	OR and 95% CI[a]	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)[a]	*P* value[a]
Standard cytogenetic risk		95/149 (63.8)	57/149 (38.3)	2.84 (1.78-4.54)	<0.0001
High cytogenetic risk		12/25 (48.0)	8/27 (29.6)	2.19 (0.67-7.17)	0.2496
Revised standard cytogenetic risk		64/94 (68.1)	34/90 (37.8)	3.51 (1.91-6.45)	<0.0001
Revised high cytogenetic risk		46/83 (55.4)	23/84 (27.1)	1.80 (0.66-3.88)	0.3895
Gain(1q)		24/43 (55.8)	22/48 (45.8)	1.49 (0.65-3.41)	0.4034
Amp(1q)		17/31 (54.8)	9/20 (45.0)	1.48 (0.48-4.59)	0.5725
1 revised HRCA		38/66 (57.6)	30/72 (41.7)	1.90 (0.97-3.74)	0.0880
≥2 revised HRCAs		8/17 (47.1)	8/12 (66.7)	0.44 (0.10-2.06)	0.4515
Isolated gain(1q)		21/35 (60.0)	17/40 (42.5)	2.03 (0.81-5.10)	0.1669
Isolated amp(1q)		13/23 (56.5)	6/17 (35.3)	2.38 (0.65-8.67)	0.2164
Isolated gain/amp(1q)		34/58 (58.6)	23/57 (40.4)	2.09 (1.00-4.41)	0.0628
Gain/amp(1q) plus ≥1 HRCA		7/16 (43.8)	8/11 (72.7)	0.29 (0.06-1.53)	0.2388

B. ≥12-month sustained MRD negativity

	OR and 95% CI[a]	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)[a]	*P* value[a]
Standard cytogenetic risk		76/149 (51.0)	38/149 (25.5)	3.04 (1.87-4.96)	<0.0001
High cytogenetic risk		10/25 (40.0)	10/27 (37.0)	1.13 (0.37-3.47)	1.0000
Revised standard cytogenetic risk		51/94 (54.3)	22/90 (24.4)	3.67 (1.95-6.88)	<0.0001
Revised high cytogenetic risk		36/83 (43.4)	25/84 (29.8)	1.81 (0.95-3.42)	0.0782
Gain(1q)		16/43 (37.2)	13/48 (27.1)	1.60 (0.66-3.88)	0.3895
Amp(1q)		15/31 (48.4)	6/20 (30.0)	2.19 (0.67-7.17)	0.2496
1 revised HRCA		30/66 (45.5)	21/72 (29.2)	2.02 (1.00-4.08)	0.0539
≥2 revised HRCAs		6/17 (35.3)	4/12 (33.3)	1.09 (0.23-5.19)	1.0000
Isolated gain(1q)		14/35 (40.0)	11/40 (27.5)	1.76 (0.67-4.63)	0.3277
Isolated amp(1q)		12/23 (52.2)	4/17 (23.5)	3.55 (0.89-14.20)	0.1043
Isolated gain/amp(1q)		26/58 (44.8)	15/57 (26.3)	2.28 (1.04-4.98)	0.0515
Gain/amp(1q) plus ≥1 HRCA		5/16 (31.3)	4/11 (36.4)	0.80 (0.16-4.02)	1.0000

C. ≥24-month sustained MRD negativity

	OR and 95% CI[a]	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)[a]	*P* value[a]
Standard cytogenetic risk		61/149 (40.9)	32/149 (21.5)	2.53 (1.52-4.22)	0.0004
High cytogenetic risk		8/25 (32.0)	8/27 (29.6)	1.12 (0.34-3.63)	1.0000
Revised standard cytogenetic risk		41/94 (43.6)	16/90 (17.8)	3.58 (1.82-7.04)	0.0002
Revised high cytogenetic risk		28/83 (33.7)	23/84 (27.4)	1.35 (0.70-2.62)	0.4042
Gain(1q)		12/43 (27.9)	13/48 (27.1)	1.04 (0.41-2.62)	1.0000
Amp(1q)		11/31 (35.5)	6/20 (30.0)	1.28 (0.38-4.29)	0.7672
1 revised HRCA		24/66 (36.4)	19/72 (26.4)	1.59 (0.77-3.29)	0.2697
≥2 revised HRCAs		4/17 (23.5)	4/12 (33.3)	0.62 (0.12-3.18)	0.6828
Isolated gain(1q)		11/35 (31.4)	11/40 (27.5)	1.21 (0.45-3.27)	0.8014
Isolated amp(1q)		9/23 (39.1)	4/17 (23.5)	2.09 (0.52-8.46)	0.3326
Isolated gain/amp(1q)		20/58 (34.5)	15/57 (26.3)	1.47 (0.66-3.28)	0.4187
Gain/amp(1q) plus ≥1 HRCA		3/16 (18.8)	4/11 (36.4)	0.40 (0.07-2.34)	0.3913

MRD, minimal residual disease; CR, complete response; OR, odds ratio; CI, confidence interval; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; amp, amplification; HRCA, high-risk cytogenetic abnormality.
[a]Martel-Haenszel estimate of the common OR is used; *P* value from Fisher's exact test.

Figure 3: Overall and sustained MRD-negative (10^{-6}) ≥CR rates

A. Overall MRD negativity

	OR and 95% CI[a]	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)[a]	*P* value[a]
Standard cytogenetic risk		71/149 (47.7)	37/149 (24.8)	2.76 (1.69-4.50)	<0.0001
High cytogenetic risk		8/25 (32.0)	12/27 (44.4)	0.59 (0.19-1.83)	0.4039
Revised standard cytogenetic risk		48/94 (51.1)	23/90 (25.6)	3.04 (1.63-5.67)	0.0005
Revised high cytogenetic risk		34/83 (41.0)	25/84 (29.8)	1.64 (0.86-3.11)	0.1470
Gain(1q)		18/43 (41.9)	15/48 (31.3)	1.58 (0.67-3.74)	0.3829
Amp(1q)		13/31 (41.9)	5/20 (25.0)	2.17 (0.63-7.47)	0.2471
1 revised HRCA		29/66 (43.9)	18/72 (25.0)	2.35 (1.14-4.84)	0.0208
≥2 revised HRCAs		5/17 (29.4)	7/12 (58.3)	0.30 (0.06-1.40)	0.1479
Isolated gain(1q)		15/35 (42.9)	11/40 (27.5)	1.98 (0.75-5.19)	0.2246
Isolated amp(1q)		11/23 (47.8)	2/17 (11.8)	6.88 (1.27-37.15)	0.0204
Isolated gain/amp(1q)		26/58 (44.8)	13/57 (22.8)	2.75 (1.23-6.16)	0.0178
Gain/amp(1q) plus ≥1 HRCA		5/16 (31.3)	7/11 (63.6)	0.26 (0.05-1.31)	0.1302

B. ≥12-month sustained MRD negativity

	OR and 95% CI[a]	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)[a]	*P* value[a]
Standard cytogenetic risk		52/149 (34.9)	22/149 (14.8)	3.09 (1.76-5.44)	<0.0001
High cytogenetic risk		4/25 (16.0)	8/27 (29.6)	0.45 (0.12-1.75)	0.3293
Revised standard cytogenetic risk		33/94 (35.1)	12/90 (13.3)	3.52 (1.68-7.38)	0.0006
Revised high cytogenetic risk		23/83 (27.7)	17/84 (20.2)	1.51 (0.74-3.10)	0.2811
Gain(1q)		12/43 (27.9)	9/48 (18.8)	1.68 (0.63-4.49)	0.3291
Amp(1q)		9/31 (29.0)	4/20 (20.0)	1.64 (0.43-6.26)	0.5292
1 revised HRCA		21/66 (31.8)	13/72 (18.1)	2.12 (0.96-4.68)	0.0758
≥2 revised HRCAs		2/17 (11.8)	4/12 (33.3)	0.27 (0.04-1.79)	0.1981
Isolated gain(1q)		11/35 (31.4)	7/40 (17.5)	2.16 (0.73-6.39)	0.1843
Isolated amp(1q)		8/23 (34.8)	2/17 (11.8)	4.00 (0.73-22.04)	0.1450
Isolated gain/amp(1q)		19/58 (32.8)	9/57 (15.8)	2.60 (1.06-6.38)	0.0497
Gain/amp(1q) plus ≥1 HRCA		2/16 (12.5)	4/11 (36.4)	0.25 (0.04-1.71)	0.1874

C. ≥24-month sustained MRD negativity

	OR and 95% CI[a]	D-VRd n/N (%)	VRd n/N (%)	OR (95% CI)[a]	*P* value[a]
Standard cytogenetic risk		40/149 (26.8)	18/149 (12.1)	2.67 (1.45-4.92)	0.0019
High cytogenetic risk		3/25 (12.0)	6/27 (22.2)	0.48 (0.11-2.16)	0.4690
Revised standard cytogenetic risk		26/94 (27.7)	9/90 (10.0)	3.44 (1.51-7.84)	0.0026
Revised high cytogenetic risk		17/83 (20.5)	14/84 (16.7)	1.29 (0.59-2.82)	0.5561
Gain(1q)		7/43 (16.3)	8/48 (16.7)	0.97 (0.32-2.95)	1.0000
Amp(1q)		8/31 (25.8)	3/20 (15.0)	1.97 (0.45-8.55)	0.4928
1 revised HRCA		16/66 (24.2)	11/72 (15.3)	1.77 (0.76-4.17)	0.2038
≥2 revised HRCAs		1/17 (5.9)	3/12 (25.0)	0.19 (0.02-2.08)	0.2785
Isolated gain(1q)		7/35 (20.0)	6/40 (15.0)	1.42 (0.43-4.70)	0.7610
Isolated amp(1q)		7/23 (30.4)	2/17 (11.8)	3.28 (0.59-18.36)	0.2557
Isolated gain/amp(1q)		14/58 (24.1)	8/57 (14.0)	1.95 (0.75-5.09)	0.2360
Gain/amp(1q) plus ≥1 HRCA		1/16 (6.3)	3/11 (27.3)	0.18 (0.02-2.00)	0.2729

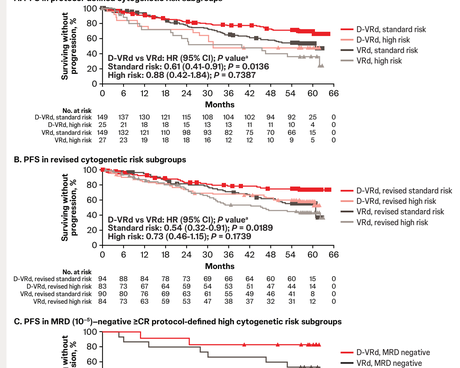
MRD, minimal residual disease; CR, complete response; OR, odds ratio; CI, confidence interval; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; amp, amplification; HRCA, high-risk cytogenetic abnormality.
[a]Martel-Haenszel estimate of the common OR is used; *P* value from Fisher's exact test.

PFS

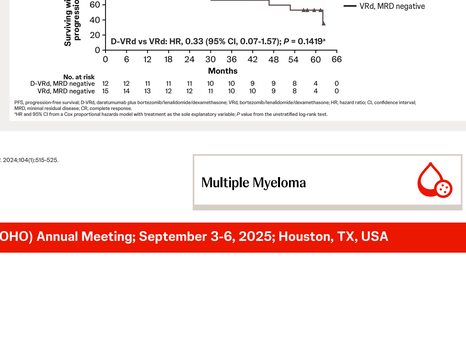
- In protocol-defined and revised standard-risk subgroups, D-VRd reduced the risk of progressive disease (PD)/death versus VRd by 39% and 46%, respectively; PFS trended in favor of D-VRd versus VRd in the protocol-defined and revised high cytogenetic risk subgroups (**Figure 4A** and **Figure 4B**)
- Among MRD-negative (10^{-5}) ≥CR revised standard cytogenetic risk subpopulations, D-VRd reduced risk of PD/death versus VRd by 37% (HR, 0.63 [95% confidence interval (CI), 0.26-1.52]; $P = 0.3003$)
- There was a trend toward improved PFS with D-VRd versus VRd in MRD-negative (10^{-5}) ≥CR patients with protocol-defined high cytogenetic risk (**Figure 4C**) and a trend favoring D-VRd versus VRd for PFS in MRD-negative (10^{-5}) ≥CR patients with revised high cytogenetic risk (HR, 0.71 [95% CI, 0.32-1.58]; $P = 0.3995$)

Figure 4: PFS in cytogenetic risk subgroups

A. PFS in protocol-defined cytogenetic risk subgroups



B. PFS in revised cytogenetic risk subgroups



C. PFS in MRD (10^{-5})–negative ≥CR protocol-defined high cytogenetic risk subgroups

PFS, progression-free survival; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; CR, complete response.
[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable; *P* value from the unstratified log-rank test.

Key Takeaway

The results of this cytogenetic subgroup analysis support use of D-VRd for TIE or TD NDMM regardless of cytogenetic risk status

Conclusions

In CEPHEUS, D-VRd consistently improved the key response outcomes of MRD negativity and PFS in patients with standard cytogenetic risk and revised standard cytogenetic risk

Consistent with associations between HRCAs and worse prognoses,[1] MRD and PFS outcomes trended lower in high- versus standard-risk subgroups in both treatment arms

In the protocol-defined high-risk subgroup, despite comparable MRD-negative ≥CR rates with D-VRd versus VRd, PFS trended toward improvement with D-VRd, supporting use of D-VRd for TIE or TD NDMM across cytogenetic risk subgroups

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Disclosure

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Multiple Myeloma

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