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Efficacy of Daratumumab-Bortezomib-Lenalidomide-Dexamethasone vs Daratumumab-Lenalidomide-Dexamethasone in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma

Saad Z Usmani[1], Thierry Facon[2], Vania Hungria[3], Nizar J Bahlis[4], Christopher P Venner[5,6], Marc Braunstein[7], Jianming He[8], Sandhya Nair[9], Andras Borsi[8], Eric M Ammann[8], Melissa Rowe[10], Robin L Carson[11], Sonja Zweegman[12]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]University of Lille, CHU de Lille, Lille, France; [3]Clínica Médica São Germano, São Paulo, Brazil; [4]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada; [5]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [6]BC Cancer–Vancouver Centre, University of British Columbia, Vancouver, BC, Canada; [7]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [8]Johnson & Johnson, Raritan, NJ, USA; [9]Johnson & Johnson, Beerse, Belgium; [10]Johnson & Johnson, High Wycombe, UK; [11]Johnson & Johnson, Spring House, PA, USA; [12]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Key Takeaway

Treatment with DVRd led to statistically significant improvements in the MRD-negative CR rate and PFS as well as an improved OS trend compared with DRd in TIE patients with NDMM aged ≤80 years

In the absence of a head-to-head trial, this indirect treatment comparison suggests deeper, more durable responses with DVRd vs DRd that may translate into improved survival outcomes, which could help inform patients and physicians when making treatment decisions in this patient population

Conclusions

For the MRD-negative CR rate, PFS, PFS2, ORR, VGPR plus rate, and CR rate, treatment with DVRd showed a statistically significant benefit over DRd

A numerical improvement in OS was observed with DVRd vs DRd. When OS rates were censored for COVID-19-related deaths, DVRd showed a statistically significant benefit over DRd

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Poster

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Disclosures

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Introduction

- There are no head-to-head clinical trials showing the comparative efficacy of daratumumab-bortezomib-lenalidomide-dexamethasone (DVRd) and daratumumab-lenalidomide-dexamethasone (DRd) in patients with transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM)
  - In the phase 3, open-label MAIA trial in patients with TIE NDMM, DRd significantly improved clinical outcomes compared with lenalidomide-dexamethasone (Rd) – a finding that led to DRd becoming a standard-of-care option for TIE NDMM[1]
  - In the phase 3, open-label CEPHEUS trial, treatment with DVRd vs bortezomib-lenalidomide-dexamethasone (VRd) showed a significantly higher minimal residual disease (MRD)-negative complete response (CR) rate and significantly improved progression-free survival (PFS) in TIE/transplant deferred patients with NDMM[2]
- The present study is an unanchored, indirect treatment comparison (ITC) of the efficacy of DVRd (CEPHEUS) and DRd (MAIA) in TIE patients with NDMM, performed using individual patient-level data

Methods

- Due to key differences in study design, population alignment was needed (**Table 1**)
  - ITC analysis sets were restricted to TIE NDMM patients aged ≤80 years at enrollment (**Table 1**). Other key inclusion/exclusion criteria were aligned across CEPHEUS and MAIA:
    - No prior systemic antimyeloma therapy; Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2; measurable disease; adequate bone marrow reserve (hemoglobin ≥7.5 g/dL; absolute neutrophil count ≥1.0 × 10^9/L, platelet count ≥70 × 10^9/L); adequate renal and liver function; and no invasive malignancy other than multiple myeloma (MM)
- TIE patients from CEPHEUS and MAIA were reweighted using inverse probability of treatment weighting – average treatment effect (IPTW-ATE) weights to balance the two treatment cohorts with respect to measured baseline patient characteristics selected a priori based on clinician input and prior publications[3]
  - Baseline covariates (**base-case model**): MM stage (per International Staging System); cytogenetic risk; age; ECOG PS; type of MM (IgG vs other); extramedullary disease; frailty (based on simplified International Myeloma Working Group frailty score); sex; estimated glomerular filtration rate (≥60 vs <60 mL/min/1.73 m^2); anemia (hemoglobin <10 vs ≥10 g/dL); lactate dehydrogenase (>280 vs ≤280 U/L)
  - Additional covariates for sensitivity analysis (**full model**): hypercalcemia (>2.75 vs ≤2.75 mmol/L); race (White vs other); time since initial MM diagnosis
- Outcomes: PFS, overall survival (OS), OS censored for COVID-19 deaths, MRD-negative CR rate, overall response rate (ORR), very good partial response rate or better (VGPR plus) rate, CR or better (CR plus) rate
  - Weighted generalized linear model (binary endpoints – OR [95% CI]), weighted Cox regression (time-to-event endpoints – HR [95% CI]) and Kaplan-Meier estimates were used

Table 1: Differences between CEPHEUS and MAIA trials and alignment of key patient inclusion/exclusion criteria

	CEPHEUS[2]	MAIA[1]
Full trial: **ITT analysis**	Overall: N=395 DVRd arm: **n=197**	Overall: N=737 DRd arm: **n=368**
Key inclusion criteria	≥18 years; transplant not intended (TIE or TD); measurable disease; ECOG PS 0–2	≥18 years; TIE due to age ≥65 y or coexisting conditions; measurable disease; ECOG PS 0–2
Key exclusion criteria	Frailty score ≥2 according to Myeloma Geriatric Assessment score (excludes patients aged >80 y)	–
Median follow- up	58.7 months	64.5 months (89.3 months for OS)
ITC analysis	TIE patients: **n=144**	Patients aged ≤80 years: **n=321**

ITT, intent-to-treat; TD, transplant deferred.

Results

Study population

- In total, 144 DVRd-treated patients (CEPHEUS; TIE subgroup) and 321 DRd-treated patients (MAIA; age ≤80 years subgroup) were included in the analysis
- Prior to reweighting, the DVRd and DRd treatment cohorts differed with respect to some baseline patient characteristics (standardized mean difference [SMD] >0.1; **Table 2**) including:
  - ISS stage I (0.17) and II (−0.16), age 70–74 years (0.14) and ≥75 years (−0.14), ECOG PS ≥2 (−0.13), extramedullary disease (0.12), frailty score (−0.12), male sex (−0.11), eGFR ≥60 mL/min/1.73 m^2 (−0.13), anemia (−0.12), and lactate dehydrogenase >280 U/L (0.21)
- After base-case IPTW, the effective sample size (ESS) decreased from 144 to 136.8 for DVRd- and 321 to 317.1 for DRd-treated patients; all SMDs were reduced to <0.1 (**Table 2**)

Clinical outcomes

- After IPTW, DVRd showed clinical benefit over DRd for most outcomes (**Table 3, Figure**)
  - For PFS, the adjusted HR for DVRd vs DRd was 0.62 (95% CI, 0.44–0.88)
  - For OS, the adjusted HR for DVRd vs DRd was 0.80 (95% CI, 0.53–1.19)
  - For OS censored for COVID-19 deaths, the adjusted OS HR for DVRd vs DRd was 0.63 (95% CI, 0.41–0.98)
  - For the MRD-negative CR rate, the adjusted odds ratio for DVRd vs DRd was 3.04 (95% CI, 2.01–4.61)
    - The adjusted MRD-negative CR rates were 61.2% for DVRd vs 34.2% for DRd

Table 2: Performance of the IPTW-adjusted indirect comparison of DVRd (CEPHEUS) vs DRd (MAIA) in the base-case model

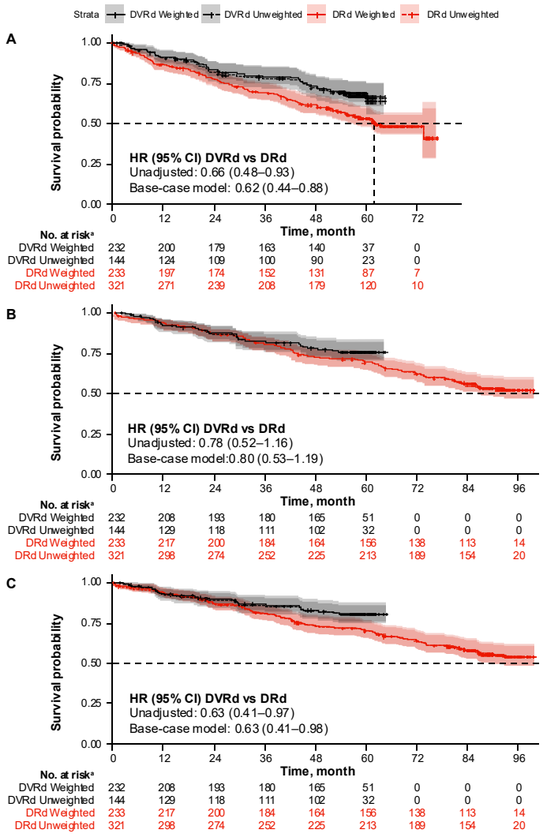
Variables	Unweighted		Weighted	
	DVRd (n=144)	DRd (n=321)	DVRd (weighted n=462.5; ESS=136.8)	DRd (weighted n=465.3; ESS=317.1)
ISS, n (%)				
I	50.0 (34.7)	87.0 (27.1)	135.2 (29.2)	136.4 (29.3)
II	54.0 (37.5)	146.0 (45.5)	198.3 (42.9)	200.2 (43.0)
III	40.0 (27.8)	88.0 (27.4)	129.0 (27.9)	128.7 (27.7)
Baseline cytogenetic profile, n (%)				
High risk	20.0 (13.9)	41.0 (12.8)	60.5 (13.1)	61.3 (13.2)
Standard risk	105.0 (72.9)	238.0 (74.1)	341.4 (73.8)	343.3 (73.8)
Missing/unknown	19.0 (13.2)	42.0 (13.1)	60.6 (13.1)	60.7 (13.1)
Age, n (%)				
≤69 years	35.0 (24.3)	78.0 (24.3)	115.5 (25.0)	113.6 (24.4)
70–74 years	68.0 (47.2)	130.0 (40.5)	202.0 (43.7)	198.9 (42.7)
≥75 years	41.0 (28.5)	113.0 (35.2)	145.0 (31.3)	152.8 (32.8)
ECOG PS, n (%)				
0	52.0 (36.1)	114.0 (35.5)	166.8 (36.1)	166.4 (35.8)
1	75.0 (52.1)	155.0 (48.3)	230.6 (49.9)	230.3 (49.5)
≥2	17.0 (11.8)	52.0 (16.2)	65.1 (14.1)	68.6 (14.8)
Type of MM at diagnosis = IgG, n (%)	92.0 (63.9)	210.0 (65.4)	291.9 (63.1)	300.1 (64.5)
Extramedullary disease, n (%)	9.0 (6.2)	12.0 (3.7)	20.7 (4.5)	20.8 (4.5)
Frailty based on simplified frailty score, n (%)	48.0 (33.3)	125.0 (38.9)	165.8 (35.8)	171.8 (36.9)
Male, n (%)	65.0 (45.1)	162.0 (50.5)	227.5 (49.2)	227.6 (48.9)
Estimated GFR <60mL/min/1.73 m^2, n(%)	47.0 (32.6)	125.0 (38.9)	169.3 (36.6)	172.0 (37.0)
Anemia, hemoglobin <10 g/dL, n (%)	45.0 (31.2)	119.0 (37.1)	156.3 (33.8)	163.3 (35.1)
Lactate dehydrogenase >280 U/L, n (%)	29.0 (20.1)	64.0 (19.9)	89.1 (19.3)	91.9 (19.8)

GFR, glomerular filtration rate; IMWG, International Myeloma Working Group; ISS, International Staging System; SMD, standardized mean difference.

Table 3: Comparison of DVRd vs DRd for all outcomes: Unadjusted analysis and IPTW adjusted base-case and full models

	PFS HR (95% CI)	PFS2 HR (95% CI)	OS HR (95% CI)	OS censored for COVID-19 deaths, HR (95% CI)	MRD-negative CR OR (95% CI)	ORR OR (95% CI)	VGPR plus OR (95% CI)	CR plus OR (95% CI)
Unadjusted	0.66 (0.48–0.93)	0.67 (0.45–0.99)	0.78 (0.52–1.16)	0.63 (0.41–0.97)	2.93 (1.95–4.39)	4.72 (1.09–20.46)	2.97 (1.42–6.19)	3.59 (2.25–5.73)
Base case	0.62 (0.44–0.88)	0.67 (0.44–1.00)	0.80 (0.53–1.19)	0.63 (0.41–0.98)	3.04 (2.01–4.61)	5.01 (1.11–22.71)	3.09 (1.45–6.61)	3.58 (2.21–5.79)
Full model	0.62 (0.43–0.88)	0.66 (0.44–1.00)	0.81 (0.54–1.22)	0.65 (0.41–1.02)	3.07 (2.01–4.69)	6.12 (1.36–27.51)	3.32 (1.50–7.31)	3.67 (2.25–6.01)

Figure: (A) PFS; (B) OS; and (C) OS censored for COVID-19 deaths for unadjusted and IPTW base-case comparisons of DVRd vs DRd



[a]The number at risk is adjusted by weight

Limitations

- There was a lack of common treatment arms across the trials; therefore, an unanchored comparison was conducted
- The impact of COVID-19 on the CEPHEUS trial introduced additional complexity when interpreting survival outcomes, though this was addressed using COVID-adjusted analyses
- The inability to adjust for certain variables that were not consistently reported across trials; there was a level of missing cytogenetic data
- OS data were immature at the time of analysis
- This ITC focused on efficacy outcomes; safety should also be considered in treatment selection
- As with any ITC, there is the potential for unmeasured confounding factors

References

1. Facon T, et al. *N Engl J Med* 2019;380:2104–15. 2. Usmani SZ, et al. *Nat Med* 2025;31:1195–1202. 3. He J, et al. *J Comp Eff Res* 2026;Aug 12:e240180. doi: 10.57264/cer-2024-0180.

Multiple Myeloma