PS1730

Daratumumab Plus Bortezomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma: Subgroup Analysis of Transplant-Ineligible Patients in the Phase 3 CEPHEUS Study

Thierry Facon[1], Sonja Zweegman[2], Vania Hungria[3], Nizar J Bahlis[4], Christopher P Venner[5], Marc Braunstein[6], Ludek Pour[7], Josep Maria Marti Tutusaus[8], Supratik Basu[9], Yaël C Cohen[10], Morio Matsumoto[11], Kenshi Suzuki[12], Cyrille Hulin[13], Sebastian Grosicki[14], Meral Beksac[15], Angelo Maiolino[16], Jianping Wang[17], Emilie van Brummelen[18], Lorena Lopez-Masi[19], Jodi Carey[20], Melissa Rowe[21], Robin L Carson[17], Saad Z Usmani[22]

[1]University of Lille, CHU de Lille, Lille, France; [2]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [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]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [7]University Hospital Brno; Masaryk University, Brno, Czech Republic; [8]Hospital Universitario Mútua de Terrassa, Terrassa, Spain; [9]Royal Wolverhampton NHS Trust and University of Wolverhampton, CRN West Midlands, NIHR, Wolverhampton, UK; [10]Tel-Aviv Sourasky (Ichilov) Medical Center; Faculty of Medical & Health Sciences, Tel Aviv University, Tel-Aviv, Israel; [11]National Hospital Organization Shibukawa Medical Center, Gunma, Japan; [12]Japanese Red Cross Medical Center, Tokyo, Japan; [13]Hôpital Haut Lévêque, University Hospital, Pessac, France; [14]Medical University of Silesia, Katowice, Poland; [15]Istinye University, Ankara University, Ankara, Türkiye; [16]Instituto Americas de Ensino, Pesquisa e Inovação, Rio de Janeiro, Brazil; [17]Johnson & Johnson, Spring House, PA, USA; [18]Johnson & Johnson, Leiden, Netherlands; [19]Johnson & Johnson, Raritan, NJ, USA; [20]Johnson & Johnson, Spring House, PA, USA, at the time that the work was performed; [21]Johnson & Johnson, High Wycombe, UK; [22]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Key Takeaway

Results of this post hoc CEPHEUS TIE subgroup analysis reinforce DVRd as standard-of-care for the treatment of TIE NDMM

Conclusions

- DVRd improved depth and duration of response in CEPHEUS patients with TIE NDMM as measured by overall MRD-negativity, 12-month sustained MRD-negativity, and 24-month sustained MRD-negativity
- Risk of disease progression or death was 49% lower for DVRd vs VRd (HR, 0.51), with higher proportion of patients alive and progression-free at 4.5 years
- Trends toward improved OS (HR, 0.66), especially when censoring for death due to COVID-19 (HR, 0.55)
- No additional safety concerns compared with the ITT population in this older TIE subgroup

Please scan QR code

Poster

https://www.congresshub.com/EHA2025/Oncology/Daratumumab/Facon

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Acknowledgments
The authors and Johnson & Johnson thank the patients who participated in this study, the staff members at the study sites, the data and safety monitoring committee, and the staff members involved in data collection and analyses. This study was funded by Johnson & Johnson. Medical writing support was provided by Shuang Li, PhD, CMPP, of Eloquent Scientific Solutions, and funded by Johnson & Johnson.

Disclosures
TF has a consulting/advisory role in Amgen, Celgene, Johnson & Johnson, Karyopharm, Oncopeptides, Roche, Sanofi, and Takeda and received speaking fees from Celgene, Johnson & Johnson, and Takeda.

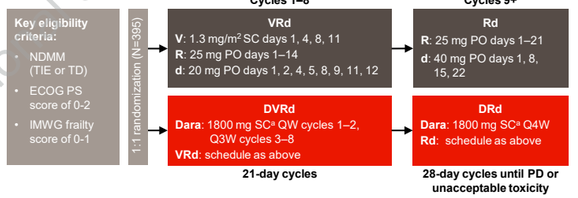
Introduction

- Daratumumab-containing triplet and quadruplet regimens, eg, daratumumab plus lenalidomide and dexamethasone (DRd) and daratumumab plus bortezomib, lenalidomide, and dexamethasone (DVRd), have demonstrated improved survival benefit in patients with newly diagnosed multiple myeloma (NDMM)[1-4]
  - DVRd is a recommended option for the treatment of transplant-eligible (TE)[5-7] and transplant-ineligible (TIE) NDMM[6-8]
  - The phase 3 MAIA trial (NCT02252172) showed significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) with DRd vs Rd for patients with TIE NDMM,[3] a population for which DRd remains a recommended treatment option[5-7]
  - The European Commission recently approved DVRd for the treatment of adult patients with NDMM regardless of transplant eligibility,[8,9] offering the opportunity for deeper responses and improved outcomes for TIE patients unable to tolerate bortezomib
- In the phase 3 CEPHEUS trial (NCT03652064), DVRd improved overall minimal residual disease (MRD)-negativity rates and PFS vs VRd in patients with NDMM who were TIE or who deferred transplant[4]
  - A subgroup analysis of CEPHEUS also demonstrated a consistent benefit of DVRd vs VRd regardless of frailty status[10]
- Transplant deferral is not a common clinical pathway for NDMM in many regions, and the majority of patients enrolled in CEPHEUS were TIE (~75%)
- This post hoc CEPHEUS subgroup analysis evaluates the efficacy and safety outcomes of DVRd in patients with TIE NDMM

Methods

- CEPHEUS is a randomized, open-label, multicenter phase 3 trial (**Figure 1**)
  - Patients: TIE or transplant-deferred (TD) NDMM
    - Randomization 1:1 to DVRd or VRd
    - Stratified by disease stage per International Staging System (ISS) and age/transplant eligibility (<70 years ineligible, <70 years refusal to transplant, ≥70 years)
- Overall MRD-negativity rate (with ≥CR) and sustained MRD negativity ≥12 and ≥24 months at 10^{-5} and 10^{-6}, PFS, OS, and safety were assessed in this analysis
  - Sustained MRD negativity was defined as 2 consecutive MRD-negative reads ≥12 months (±1) or 24 months (±3) apart with no MRD positive results in between

Figure 1: Study design



Primary endpoint: Overall MRD (≥CR) negativity[b]
Key secondary endpoints: PFS, sustained MRD (≥CR) negativity (≥12 months), ≥CR rate, safety

[a]Dara 1800 mg co-formulated with recombinant human hyaluronidase PH20 (rHuPH20); 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA). [b]MRD was assessed via next-generation sequencing (clonoSEQ®; Adaptive Biotechnologies, Seattle, WA, USA) using bone marrow aspirate samples obtained at baseline; at the time of suspected CR; and at 12, 18, 24, 30, and 36 months after the first dose and annually thereafter in patients with CR. ClinicalTrials.gov identifier: NCT03652064. CR, complete response; d, dexamethasone; Dara, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; PO, oral; Q3W, every 3 weeks; Q4W, every 4 weeks; QW, weekly; R, lenalidomide; Rd, lenalidomide and dexamethasone; SC, subcutaneous; V, bortezomib; VRd, bortezomib, lenalidomide, and dexamethasone.

Results

Patients

- Of 395 patients in the intent-to-treat (ITT) population (median follow-up 58.7 months), 289 were TIE (DVRd, n=144; VRd, n=145)
  - Results of the ITT population have been published[4]
- The baseline characteristics (**Table 1**) were well balanced between treatment arms
  - In the TIE vs ITT population[4]:
    - Median age was older (72 vs 70 years)
    - A higher percentage of patients was of intermediate fitness per International Myeloma Working Group (IMWG) criteria (41.2% vs 35.2%)

MRD negativity in TIE patients

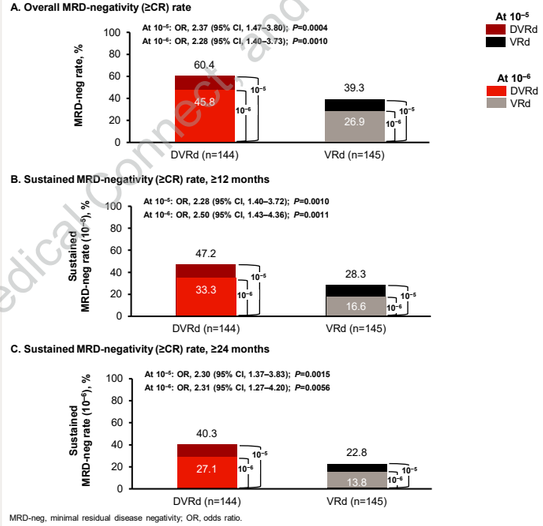
- Overall MRD-negativity (≥CR) rates significantly increased with DVRd at both 10^{-5} and 10^{-6} vs VRd (**Figure 2A**)
- Sustained MRD-negativity (≥CR) rates at both 10^{-5} and 10^{-6} are shown in **Figure 2B** (≥12 months) and **Figure 2C** (≥24 months)

Table 1: Baseline demographics and clinical characteristics

Characteristic	DVRd (n=144)	VRd (n=145)
Age		
Median (range), years	72.0 (42–79)	72.0 (31–80)
<70 years, n (%)	35 (24.3)	35 (24.1)
70 to <75 years, n (%)	68 (47.2)	65 (44.8)
≥75 years, n (%)	41 (28.5)	45 (31.0)
Male, n (%)	65 (45.1)	82 (56.6)
ECOG PS score, n (%)		
0	52 (36.1)	57 (39.3)
1	75 (52.1)	78 (53.8)
2	17 (11.8)	10 (6.9)
IMWG frailty score, n (%)		
0 (fit)	82 (56.9)	88 (60.7)
1 (intermediate fitness)	62 (43.1)	57 (39.3)
IFM frailty score, n (%)		
Nonfrail (0–1)	96 (66.7)	110 (75.9)
Frail (≥2)	48 (33.3)	35 (24.1)
Type of myeloma by immunofixation or serum FLC assay, n (%)		
IgG	92 (63.9)	78 (53.8)
IgA	26 (18.1)	42 (29.0)
IgD	2 (1.4)	2 (1.4)
Light chain	20 (13.9)	19 (13.1)
Biclonal	4 (2.8)	3 (2.1)
Unknown	0	1 (0.7)
Extramedullary plasmacytomas, n (%)	9 (6.3)	12 (8.3)
ISS staging, n (%)		
I	50 (34.7)	48 (33.1)
II	54 (37.5)	57 (39.3)
III	40 (27.8)	40 (27.6)
Cytogenetic risk, n (%)[a]		
Standard	105 (72.9)	111 (76.6)
High	20 (13.9)	18 (12.4)
Unevaluable or missing	19 (13.2)	16 (11.0)

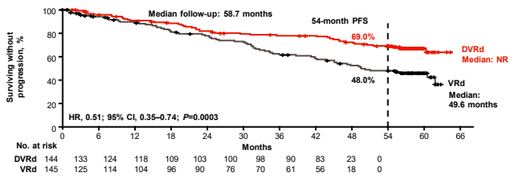
[a]Based on fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16). IFM, Intergroupe Francophone du Myelome; Ig, immunoglobulin.

Figure 2: Overall and sustained MRD-negativity (≥CR) rates



MRD-neg, minimal residual disease negativity; OR, odds ratio.

Figure 3: PFS



HR, hazard ratio.

PFS and OS

- DVRd significantly improved PFS, with a 49% reduction in the risk of disease progression or death – greater than the ITT population (43% reduction in risk with DVRd vs VRd)[4] (**Figure 3**)
- OS trended favorably for the DVRd arm (HR, 0.66; **Figure 4A**), especially when censoring for death due to COVID-19 (HR, 0.55; 95% CI, 0.34–0.90) (**Figure 4B**)
  - OS HR improved in the TIE subgroup compared with the ITT population (HR, 0.85; censoring for death due to COVID-19, HR, 0.55)[4]
- As measured by overall MRD-negativity rate and PFS, treatment effect was generally consistent across prespecified subgroups in the CEPHEUS TIE subpopulation (**Figure 5**)

Safety

- DVRd showed no additional safety concerns in this older TIE subgroup compared with the ITT population of CEPHEUS (**Table 2**)
  - The rates of non–COVID-19 grade 5 treatment-emergent adverse events (TEAEs) were similar in both DVRd and VRd groups (**Table 2**)
  - In the DVRd arm, the rate of grade 5 TEAEs was lower compared with the ITT population[4]

Figure 4: OS

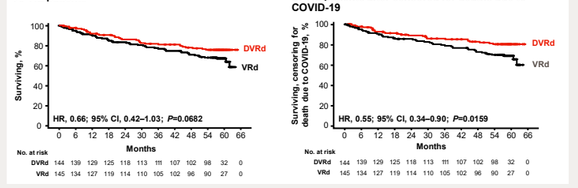
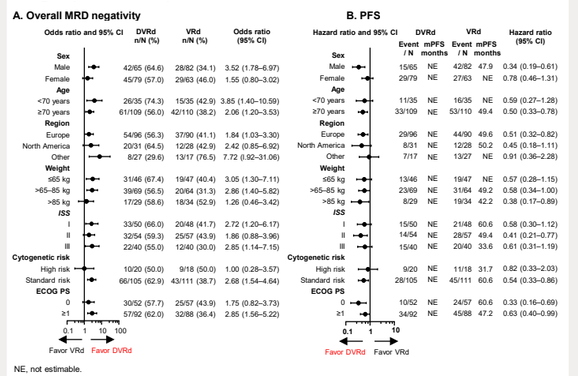


Figure 5: Overall MRD negativity (10^{-5}) with ≥CR and PFS in prespecified subgroups of the TIE patients



NE, not estimable.

Table 2: Safety overview and common (≥5%) grade 3 or 4 TEAEs of interest

Event, n (%)	DVRd (n=144)	VRd (n=142)
Any TEAE	144 (100)	142 (100)
Grade 3 and 4	115 (79.9)	113 (79.6)
Grade 5 non–COVID-19	13 (9.0)	12 (8.5)
Grade 5 COVID-19[a]	6 (4.2)	1 (0.7)
Any serious TEAE	104 (72.2)	99 (69.7)
TEAE leading to discontinuation of all study treatment	11 (7.6)	27 (19.0)
Total deaths during study	33 (22.9)	46 (32.4)
Exposure-adjusted Grade 5 TEAE rate, patient-months	0.27/100	0.31/100
Second primary malignancies	15 (7.6)	18 (9.2)
Common (≥5%) Grade 3 or 4 TEAEs of interest	**DVRd (n=144)**	**VRd (n=142)**
Neutropenia	63 (43.8)	45 (31.7)
Thrombocytopenia	44 (30.6)	33 (23.2)
Anemia	18 (12.5)	18 (12.7)
Diarrhea	17 (11.8)	14 (9.9)
Fatigue	13 (9.0)	15 (10.6)
COVID-19[b]	14 (9.7)	5 (3.5)
Pneumonia	20 (13.9)	17 (12.0)
Peripheral sensory neuropathy	Any Grade: 86 (59.7) Grade 3/4: 14 (9.7)	Any Grade: 90 (63.4) Grade 3/4: 12 (8.5)

[a]Deaths on or within 30 days of treatment. [b]Group term.

References
1. Facon, T. et al. *N Engl J Med* 2019;380:2104-15. 2. Sonneveld P, et al. *N Engl J Med* 2024;390:301-13. 3. Facon T, et al. *Leukemia* 2025;39:942-50. 4. Usmani, SZ, et al. *Nat Med*. 2025;31:1195–1202. 5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.2.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed May 5, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 6. Rajkumar SV. *Am J Hematol* 2024;99:1802-24. 7. mSMART. Treatment for Multiple Myeloma v22. 8. European Medicines Agency. Darzalex: EPAR - Product Information. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf. 9. DARZALEX® (daratumumab). Summary of product characteristics. Leiden, Netherlands: Janssen Biologics BV; 2025. 10. Zweegman S, et al. Presented at the 6th European Myeloma Network (EMN) Meeting; April 10, 2025; Athens, Greece.

Multiple Myeloma

Presented by T Facon at the European Hematology Association (EHA) 2025 Hybrid Congress; June 12–15, 2025; Milan, Italy