MM-771

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


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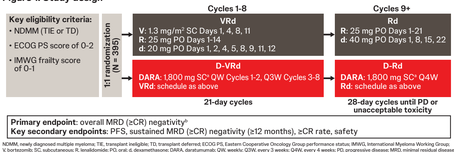

## Introduction

- Daratumumab-containing triplet and quadruplet regimens (eg, daratumumab plus lenalidomide and dexamethasone [D-Rd] and daratumumab plus bortezomib, lenalidomide, and dexamethasone [D-VRd]) have demonstrated improved survival benefit in patients with newly diagnosed multiple myeloma (NDMM)[1-4]
  - D-VRd is a recommended option for the treatment of transplant-eligible[5-7] and transplant-ineligible (TIE) NDMM[6-8]
  - The phase 3 MAIA trial (ClinicalTrials.gov Identifier: NCT02252172) showed significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) with D-Rd versus Rd for patients with TIE NDMM,[3] a population for which D-Rd remains a recommended treatment option[5-7]
  - The European Commission recently approved D-VRd 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 who are unable to tolerate bortezomib
- In the phase 3 CEPHEUS trial (ClinicalTrials.gov Identifier: NCT03652064), D-VRd improved overall minimal residual disease (MRD)–negativity rates and PFS versus VRd in patients with NDMM who were TIE or who deferred transplant[4]
  - A subgroup analysis of CEPHEUS also demonstrated a consistent benefit of D-VRd versus 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 D-VRd in patients with TIE NDMM

## Methods

- CEPHEUS is a randomized, open-label, multicenter phase 3 trial (**Figure 1**)
  - Patients: TIE or transplant-deferred NDMM
    - Randomization 1:1 to D-VRd 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 (with complete response or better [≥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[a]
**Key secondary endpoints**: PFS, sustained MRD (≥CR) negativity (≥12 months), ≥CR rate, safety

NDMM, newly diagnosed multiple myeloma; TIE, transplant ineligible; TD, transplant deferred; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; NCT, National Clinical Trial; V, bortezomib; R, lenalidomide; d, dexamethasone; DARA, daratumumab; QW, weekly; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; PO, by mouth; SC, subcutaneous; 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.).
[a]MRD was assessed via next-generation sequencing (clonoSEQ®; Adaptive Biotechnologies) 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.

## Results

### Patients

- Of 395 patients in the intent-to-treat (ITT) population (median follow-up, 58.7 months), 289 were TIE (D-VRd, 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 versus ITT population[4]:
    - Median age was older (72 vs 70 years, respectively)
    - A higher percentage of patients was of intermediate fitness per International Myeloma Working Group (IMWG) criteria (41.2% vs 35.2%, respectively)

### MRD negativity in TIE patients

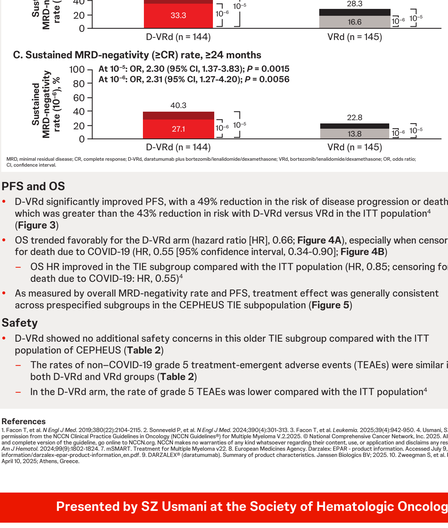
- Overall MRD-negativity (≥CR) rates significantly increased with D-VRd at both $10^{-5}$ and $10^{-6}$ versus VRd (**Figure 2A**)
- Sustained MRD-negativity (≥CR) rates at both $10^{-5}$ and $10^{-6}$ are shown in **Figure 2B** (≥12 months) and **Figure 2C** (≥24 months)

**Table 1: Baseline demographic and clinical characteristics**

| Characteristic | D-VRd (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 (%)*** | | |
| Standard | 105 (72.9) | 111 (76.6) |
| High | 20 (13.9) | 18 (12.4) |
| Unevaluable or missing | 19 (13.2) | 16 (11.0) |

D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; IFM, Intergroupe Francophone du Myelome; FLC, free light chain; Ig, immunoglobulin; ISS, International Staging System.
*Based on fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

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




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

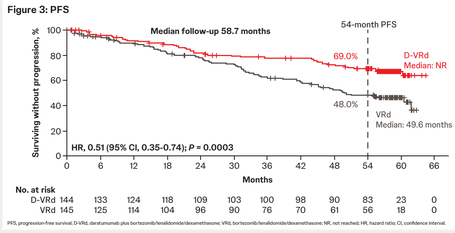
### PFS and OS

- D-VRd significantly improved PFS, with a 49% reduction in the risk of disease progression or death, which was greater than the 43% reduction in risk with D-VRd versus VRd in the ITT population[4] (**Figure 3**)
- OS trended favorably for the D-VRd arm (hazard ratio [HR], 0.66; **Figure 4A**), especially when censoring for death due to COVID-19 (HR, 0.55 [95% confidence interval, 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

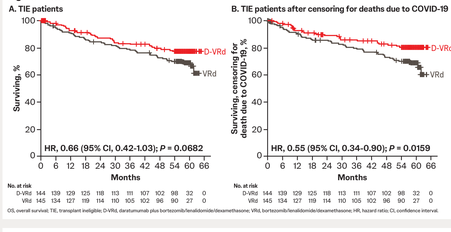
- D-VRd showed no additional safety concerns in this older TIE subgroup compared with the ITT population of CEPHEUS (**Table 2**)
  - The rates of non–COVID-19 grade 5 treatment-emergent adverse events (TEAEs) were similar in both D-VRd and VRd groups (**Table 2**)
  - In the D-VRd arm, the rate of grade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

**Figure 3: PFS**



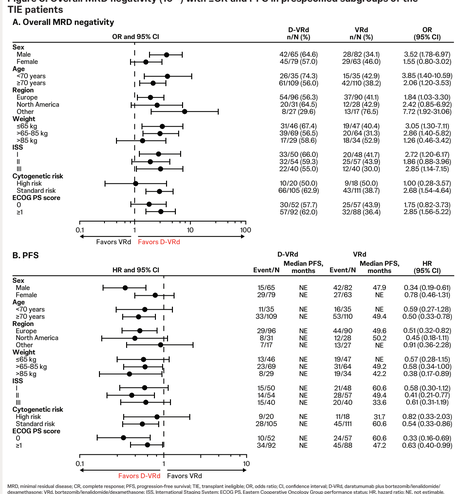

PFS, progression-free survival; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; NR, not reached; HR, hazard ratio; CI, confidence interval.

**Figure 4: OS**




OS, overall survival; TIE, transplant ineligible; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

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




MRD, minimal residual disease; CR, complete response; PFS, progression-free survival; TIE, transplant ineligible; OR, odds ratio; CI, confidence interval; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; ISS, International Staging System; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NE, not estimable.

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

| Event, n (%) | D-VRd (n = 144) | VRd (n = 142) |
|---|---|---|
| **Any TEAE** | 144 (100) | 142 (100) |
| Grades 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** | **D-VRd (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[a]** | 14 (9.7) | 5 (3.5) |
| **Pneumonia** | 20 (13.9) | 17 (12.0) |
| **Peripheral sensory neuropathy** | Any grade: 86 (59.7)<br>Grade 3/4: 14 (9.7) | Any grade: 90 (63.4)<br>Grade 3/4: 12 (8.5) |

TEAE, treatment-emergent adverse event; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.
[a]Deaths on or within 30 days of treatment.
[b]Group term.

## Key Takeaway

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

## Conclusions

D-VRd 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 D-VRd versus VRd (HR, 0.51), with a higher proportion of patients alive and progression-free at 4.5 years

Trends toward improved OS with D-VRd versus VRd (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


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Multiple Myeloma

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