MM-338

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

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Key Takeaway

The final CEPHEUS analysis results reinforce D-VRd as the standard of care for patients with TIE NDMM as it provides deeper and more durable responses than VRd

Conclusions

- After a median follow-up of over 6 years, the final analysis of the CEPHEUS trial demonstrated that D-VRd continues to show superior efficacy over VRd across key endpoints in TIE patients
- In this post hoc analysis, D-VRd improved depth of response versus VRd, with higher overall MRD negativity at the 10^{-5} threshold (61.1% vs 40.0%; OR, 2.35) and 10^{-6} threshold (46.5% vs 27.6%; OR, 2.27)
- D-VRd also improved the rates of sustained MRD negativity lasting ≥12 months (10^{-5}: 49.3% vs 29.0%; 10^{-6}: 37.5% vs 16.6%) and ≥24 months (10^{-5}: 44.4% vs 23.4%; 10^{-6}: 30.6% vs 15.2%)
- Risk of disease progression or death was 45% lower for D-VRd versus VRd
- OS favored D-VRd, especially when censoring for death due to COVID-19 (HR, 0.74)
- No additional safety concerns were identified with longer follow-up in this older, frailer TIE subgroup

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Disclosure

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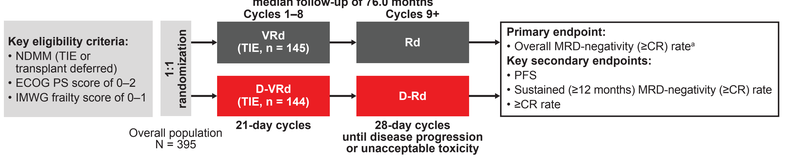
Introduction

- Daratumumab-based quadruplet therapy has transformed the newly diagnosed multiple myeloma (NDMM) treatment landscape and demonstrated improved survival outcomes for patients[1–4]
  - Daratumumab plus bortezomib, lenalidomide, and dexamethasone (D-VRd) is a recommended treatment option for transplant-eligible[5–7] and transplant-ineligible (TIE) patients with NDMM[6,7]
- The phase 3 CEPHEUS trial (ClinicalTrials.gov Identifier: NCT03652064) established D-VRd as a new standard of care for TIE and transplant-deferred patients with NDMM by demonstrating[4]:
  - Improved depth and duration of response, with higher rates of overall minimal residual disease (MRD; 10^{-5}) negativity and higher rates of sustained MRD negativity lasting 1 year and 2 years
  - Improved progression-free survival (PFS), with a higher proportion of patients alive and progression free at 4.5 years[8]
- The majority of patients (n = 289 [~75%]) enrolled in CEPHEUS were TIE—an older, frailer population (median age, 72 years, with ~76% aged ≥70 years and ~30% aged ≥75 years) versus the intent-to-treat population, with distinct clinical needs
- This final analysis of the CEPHEUS TIE subpopulation describes efficacy and safety outcomes of D-VRd in TIE patients with NDMM after a longer median follow-up of 76.0 months

Methods

- CEPHEUS is a randomized, open-label, multicenter, phase 3 study (**Figure 1**)
- The primary endpoint was overall MRD-negativity rate, defined as the proportion of patients who achieved a complete response or better (≥CR) and were MRD negative (at or below the 10^{-5} sensitivity threshold) after randomization but before progression, subsequent antimyeloma therapy, or both

Figure 1: CEPHEUS study design

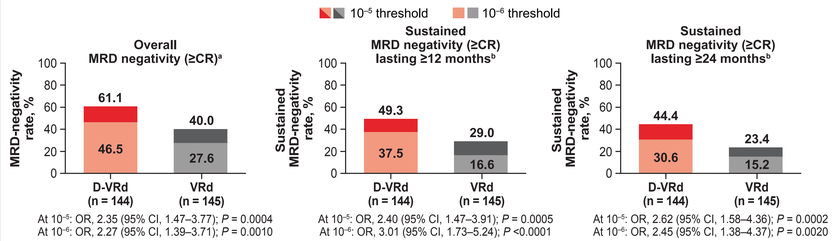


NDMM, newly diagnosed multiple myeloma; TIE, transplant ineligible; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; VRd, bortezomib, lenalidomide, and dexamethasone; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; D-Rd, daratumumab plus lenalidomide and dexamethasone; MRD, minimal residual disease; CR, complete response; PFS, progression-free survival
[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.[4]
ClinicalTrials.gov Identifier: NCT03652064.

Results

- At a median follow-up of 76.0 months, D-VRd demonstrated superior overall and sustained MRD-negativity rates at 10^{-5} and 10^{-6} versus bortezomib, lenalidomide, and dexamethasone (VRd; **Figure 2**)

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



At 10^{-5}: OR, 2.35 (95% CI, 1.47–3.77); P = 0.0004
At 10^{-6}: OR, 2.27 (95% CI, 1.39–3.71); P = 0.0010

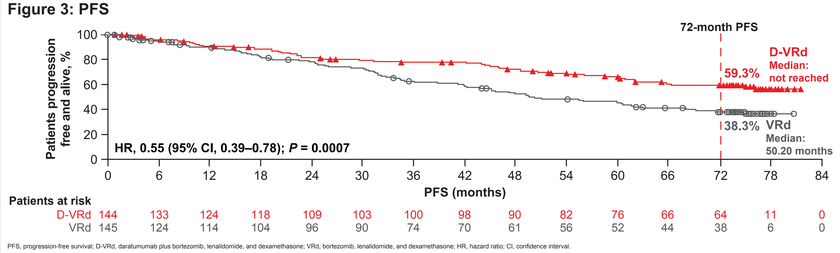
At 10^{-5}: OR, 2.40 (95% CI, 1.47–3.91); P = 0.0005
At 10^{-6}: OR, 3.01 (95% CI, 1.73–5.24); P <0.0001

At 10^{-5}: OR, 2.62 (95% CI, 1.58–4.36); P = 0.0002
At 10^{-6}: OR, 2.45 (95% CI, 1.38–4.37); P = 0.0020

MRD, minimal residual disease; CR, complete response; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; OR, odds ratio; CI, confidence interval.
The overall ≥CR rate was not changed from the primary analysis: 80.6% (D-VRd) versus 61.4% (VRd; OR, 2.64 [95% CI, 1.54–4.51]; P = 0.003).
[a]The proportion of patients who achieved MRD negativity and ≥CR.
[b]Sustained MRD negativity was defined as 2 consecutive MRD-negative reads ≥12 months (±1) or 24 months (±3) apart with no MRD-positive result in between.

- D-VRd significantly improved PFS, with a 45% reduction in the risk of disease progression or death versus VRd[4] (**Figure 3**)

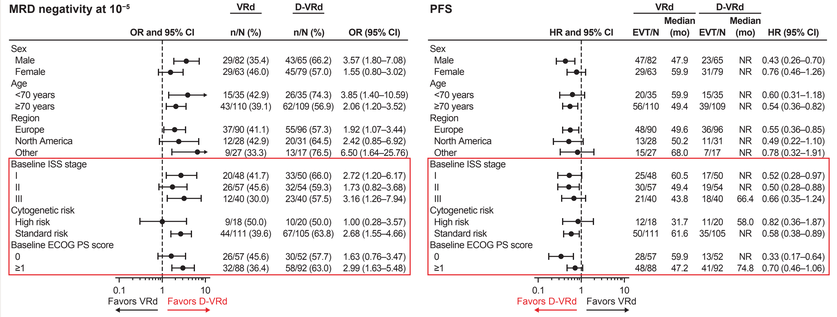
Figure 3: PFS



PFS, progression-free survival; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; CI, confidence interval.

- The treatment effect was generally consistent across subgroups, including high-risk subgroups (**Figure 4**; red box)

Figure 4: Overall MRD negativity (10^{-5}) with ≥CR and PFS in prespecified subgroups



MRD, minimal residual disease; CR, complete response; PFS, progression-free survival; OR, odds ratio; CI, confidence interval; VRd, bortezomib, lenalidomide, and dexamethasone; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; ISS, International Staging System; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; EVT, event; NR, not reached.

- D-VRd showed no additional safety concerns with longer follow-up (**Table 1** and **Table 2**)

Table 1: Safety overview

Event, n (%)	D-VRd (n = 144)	VRd (n = 142)
Any TEAE	144 (100)	142 (100)
Grade 3 or 4	135 (93.8)	126 (88.7)
Grade 5 non–COVID-19	18 (12.5)	13 (9.2)
Grade 5 COVID-19[a]	6 (4.2)	1 (0.7)
Exposure-adjusted grade 5 TEAE rate, patient-months[b]	0.30/100	0.26/100
Any serious TEAE	109 (75.7)	99 (69.7)
TEAE leading to discontinuation of all study treatment	14 (9.7)	33 (23.2)
Second primary malignancies	20 (13.9)	20 (14.1)

D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; TEAE, treatment-emergent adverse event.
[a]Deaths on or within 30 days of treatment.
[b]Exposure-adjusted incidence rate: number of patients with event per 100 patient-months at risk. Patient-months at risk = sum of exposure time until first TEAE occurrence or end of treatment for patients without the event.

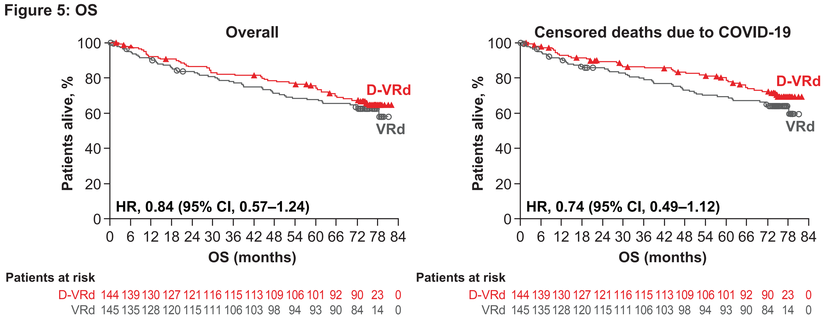
Table 2: Common (≥5%) grade 3 or 4 TEAEs of interest

Event, n (%)	D-VRd (n = 144)	VRd (n = 142)
Neutropenia	65 (45.1)	47 (33.1)
Thrombocytopenia	44 (30.6)	33 (23.2)
Anemia	16 (11.1)	14 (9.9)
Diarrhea	20 (13.9)	15 (10.6)
Fatigue	13 (9.0)	15 (10.6)
COVID-19[a]	14 (9.7)	5 (3.5)
Pneumonia	26 (18.1)	19 (13.4)
Peripheral sensory neuropathy		
Any grade	86 (59.7)	91 (64.1)
Grade 3 or 4	14 (9.7)	12 (8.5)

TEAE, treatment-emergent adverse event; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.
[a]Group term.

- Overall survival (OS) favored D-VRd, especially when censoring for death due to COVID-19 (hazard ratio [HR], 0.74; **Figure 5**)
  - The leading cause of death was unrelated adverse events (D-VRd, n = 23 [16.0%]; VRd, n = 15 [10.6%])
  - Of the total deaths in the TIE population, 11 (3.8%) were COVID-19 related (D-VRd, n = 8/144 [5.6%]; VRd, n = 3/142 [2.1%])
  - Death from progressive disease was more than double in the VRd arm (D-VRd, n = 8 [5.6%]; VRd, n = 17 [12.0%])

Figure 5: OS



OS, overall survival; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; CI, confidence interval.
The CEPHEUS study was not powered to detect a statistically significant OS difference.

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Multiple Myeloma

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