

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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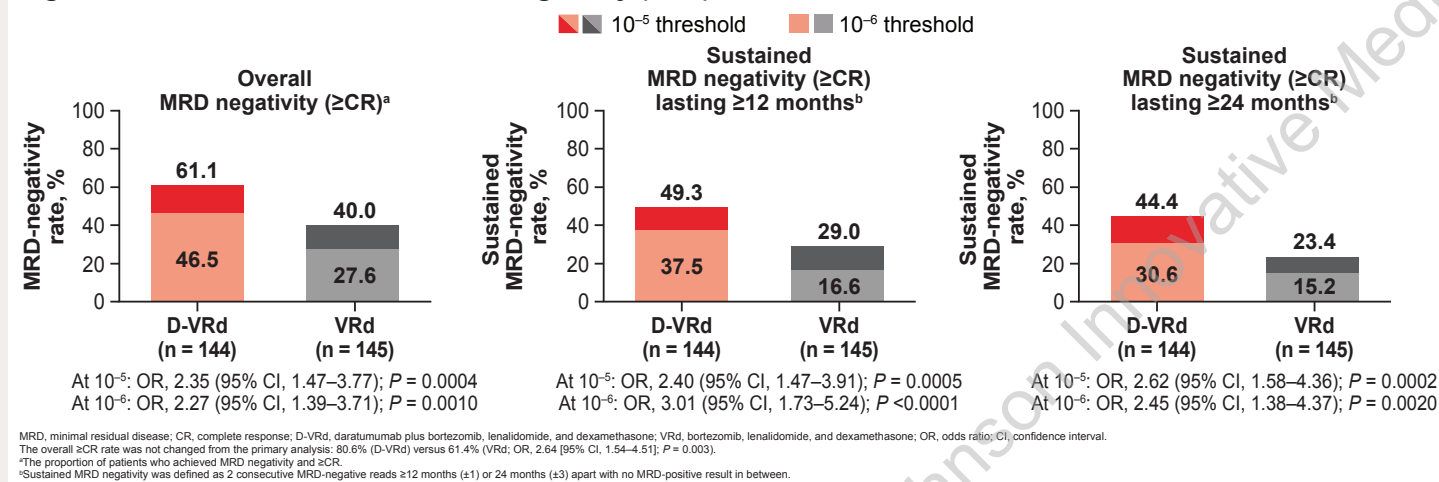
Introduction

- 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 demonstrating⁸:
 - 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 years⁸
- 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

Results

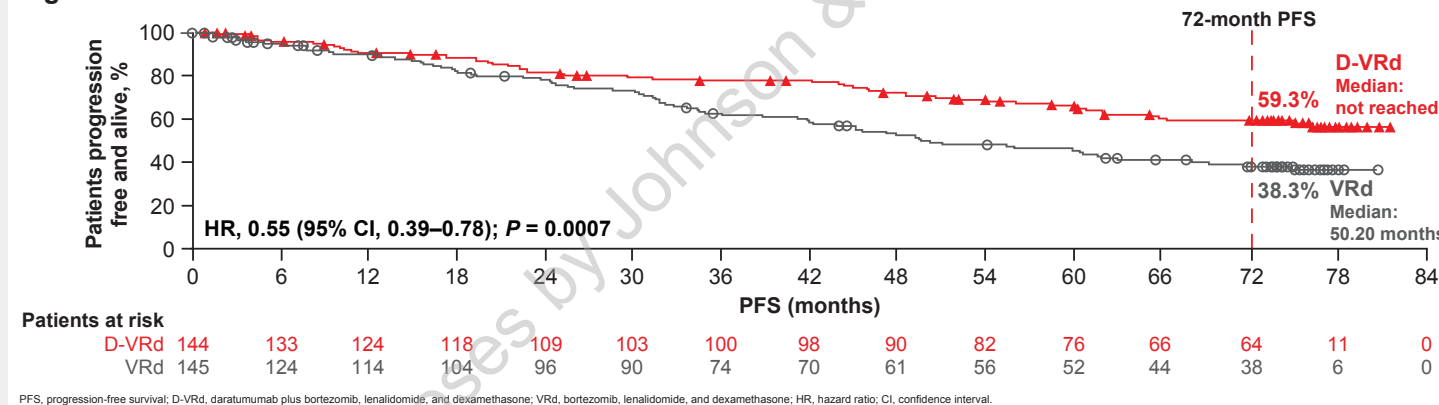
- At a median follow-up of 76.0 months, D-VRd demonstrated superior overall and sustained MRD-negativity rates at 10⁻⁵ and 10⁻⁶ versus bortezomib, lenalidomide, and dexamethasone (VRd; **Figure 2**)

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



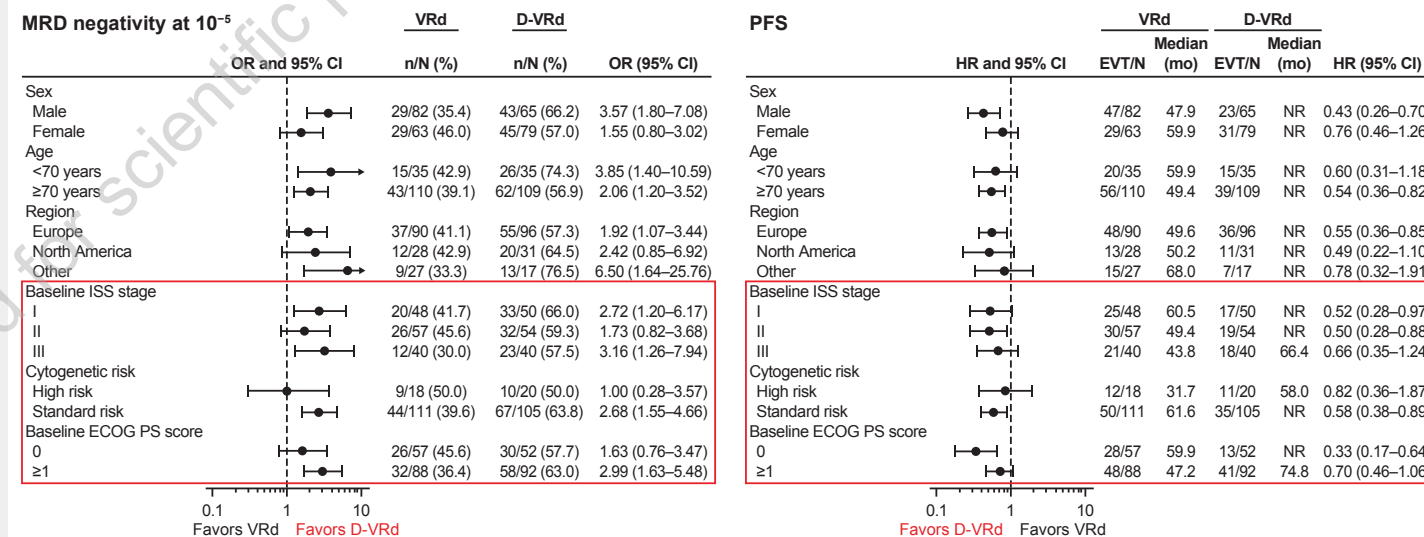
- D-VRd significantly improved PFS, with a 45% reduction in the risk of disease progression or death versus VRd⁴ (**Figure 3**)

Figure 3: PFS



- 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



References

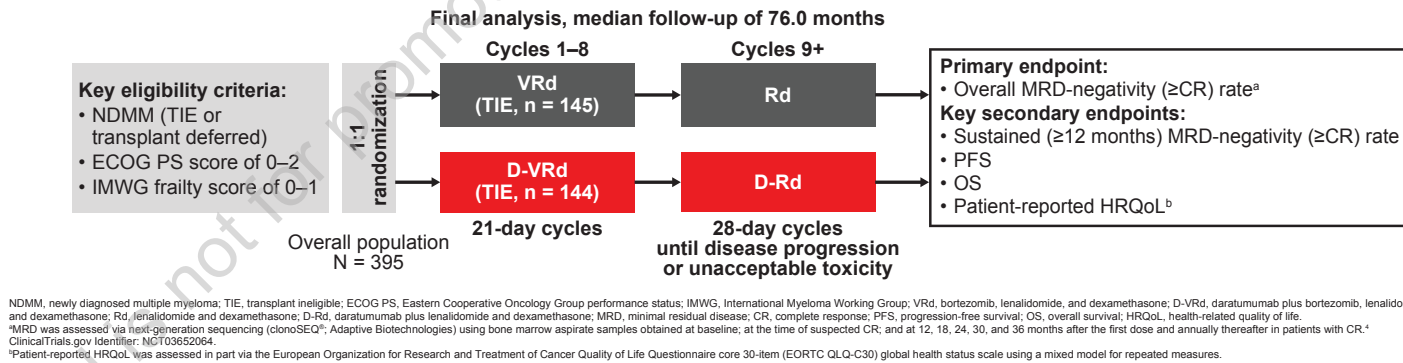
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Methods

- CEPHEUS is a randomized, open-label, multicenter, phase 3 study (**Figure 1**)

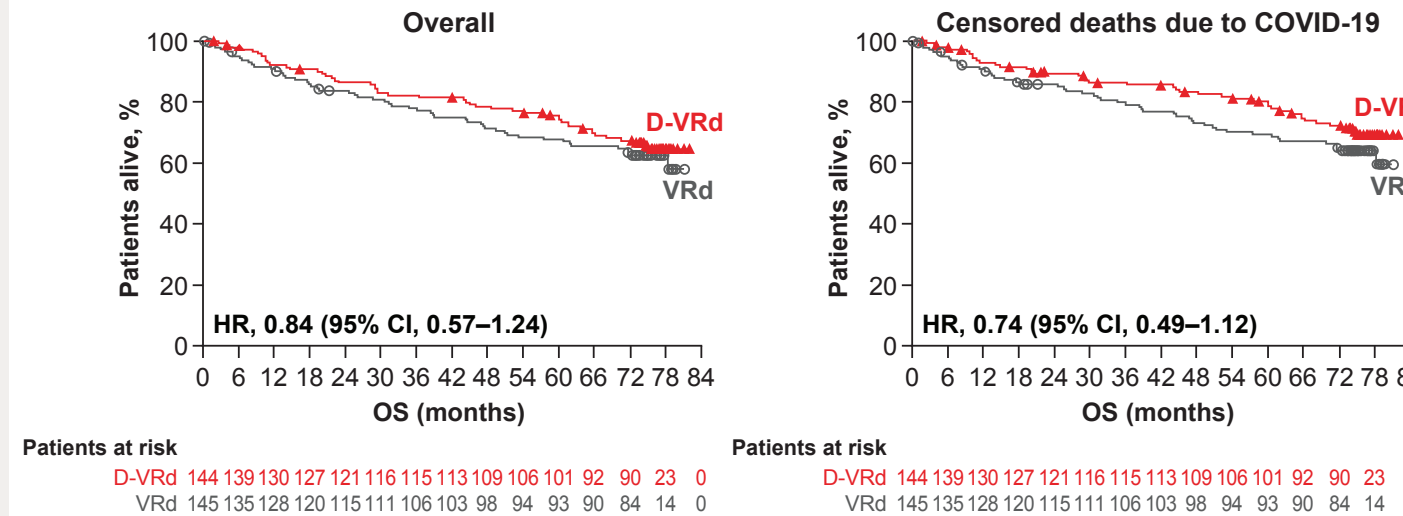
- The primary endpoint was overall MRD-negativity rate, defined as the proportion of patients who achieved a complete response or better (≥CR) and were MRD negative (at or below the 10⁻⁵ sensitivity threshold) after randomization but before progression, subsequent antimyeloma therapy, or both

Figure 1: CEPHEUS study design



- 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



- 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.

^aDeaths on or within 30 days of treatment.

^bExposure-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.

^aGroup term.

- Least squares mean change from baseline in scores for EORTC QLQ-C30 global health status, a measure of health-related quality of life (HRQoL), showed consistent improvement from baseline in both treatment groups from Cycle 9 onward
 - On Day 1 of Cycle 72, the least squares mean change from baseline in global health status was +4.1 (95% CI, 0.9–9.1) for D-VRd (n = 36) and +7.6 (95% CI, 1.6–13.6) for VRd (n = 24)

