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

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CEPHEUS TIE Final Analysis: Key Takeaways

- After median follow-up of over 6 years (76.0 months), DVRd continued to show superiority vs VRd in all key endpoints, including:
  - Durable and deep responses, with 61.1% achieving overall MRD negativity at 10^{-5} (vs. 40.0% VRd; OR 2.35; 95% CI 1.47–3.77) and a higher rate of sustained MRD negativity for ≥12 and ≥24 months
  - Nearly 60% of patients remained alive and progression-free at 72 months with DVRd, with median PFS not yet reached (vs. 50.2 months with VRd; HR 0.55; 95% CI 0.39–0.78)
  - No additional safety concerns compared with the ITT population in this older, frailer TIE subgroup

The final CEPHEUS analysis results reinforce DVRd as the standard of care for patients with TIE NDMM, providing deeper and more durable responses than those receiving VRd

DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OR, odds ratio; OS, overall survival; PFS, progression-free survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

Introduction

- Daratumumab-based quadruplet therapy has transformed the NDMM treatment landscape and demonstrated improved survival outcomes for patients[1-4]
  - DVRd is a recommended treatment option for the treatment of TE[5-7] and TIE NDMM[6,7]
- The phase 3 CEPHEUS trial established DVRd as a new standard of care in TIE and TD NDMM4:
  - Improved depth and duration of response with higher rates of overall MRD (10^{-5}) negativity and higher rates of sustained ≥1-year and ≥2-year MRD negativity
  - Improved PFS with a higher proportion of patients alive and progression-free at 4.5 years[8]
- **The majority of patients (~75%) enrolled in CEPHEUS were TIE – an older, frailer population vs ITT, with distinct clinical needs**

TIE POPULATION at BL – AGE PROFILE (n=289)

72 years
Median age

~76%
Aged ≥70 years

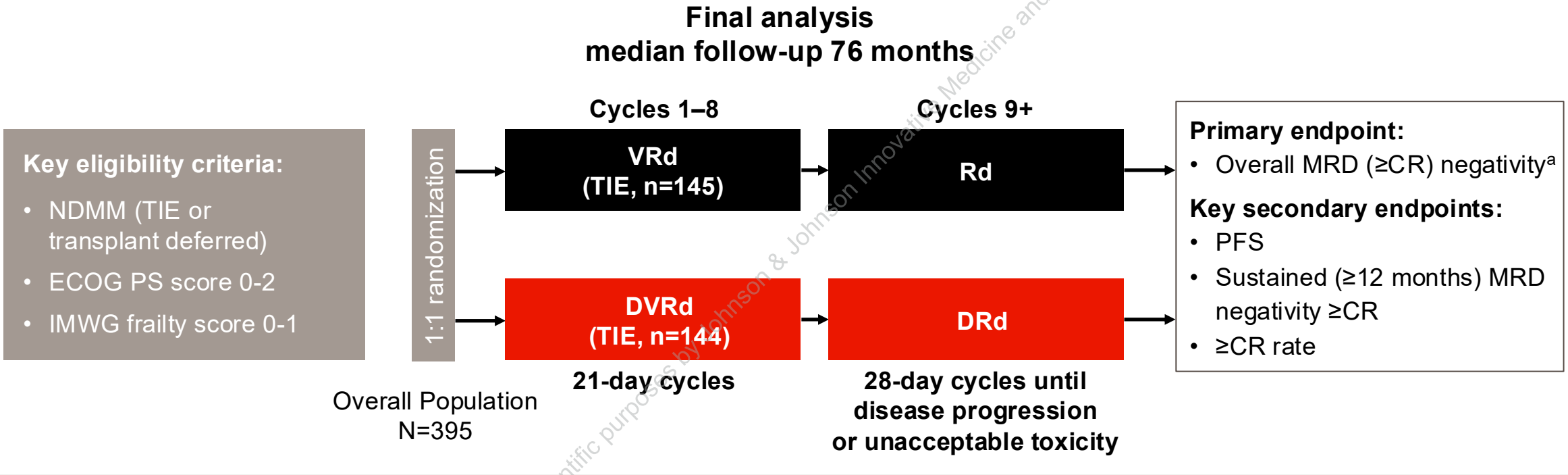
~30%
Aged ≥75 years

This final analysis of the CEPHEUS TIE subpopulation describes efficacy and safety outcomes of DVRd in TIE NDMM after a longer median follow-up of 76 months

MAIA: NCT02252172; CEPHEUS: NCT03652064. BL, baseline; DRd, daratumumab, lenalidomide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; TD, transplant deferred; TE, transplant eligible; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

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;31:1195-202.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.5.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed March 24, 2026.
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. Facon T, et al. Presented at ASCO 2025; Chicago, IL, USA.

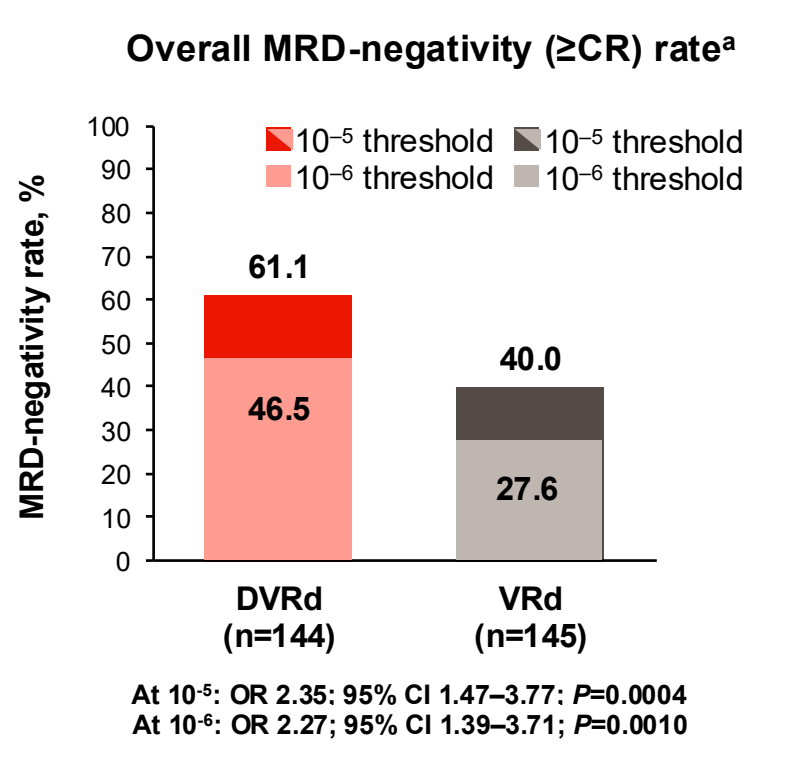
CEPHEUS: Study Design



This CEPHEUS final subgroup analysis includes only patients with TIE NDMM (~75% of the ITT population)

[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. CR, complete response; DRd, daratumumab, lenalidomide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone. ClinicalTrials.gov Identifier: NCT03652064. Accessed April 7, 2025.
Usmani, SZ, et al. *Nat Med* 2025;31:1195-202.

CEPHEUS TIE Final Analysis: Overall and Sustained MRD-Negativity ≥CR Rates



DVRd demonstrated superior overall and sustained MRD negativity rates at 10^{-5} and 10^{-6} vs VRd

The overall ≥CR rate was not changed from the primary analysis: 80.6% (DVRd) vs 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.
CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; OR, odds ratio; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

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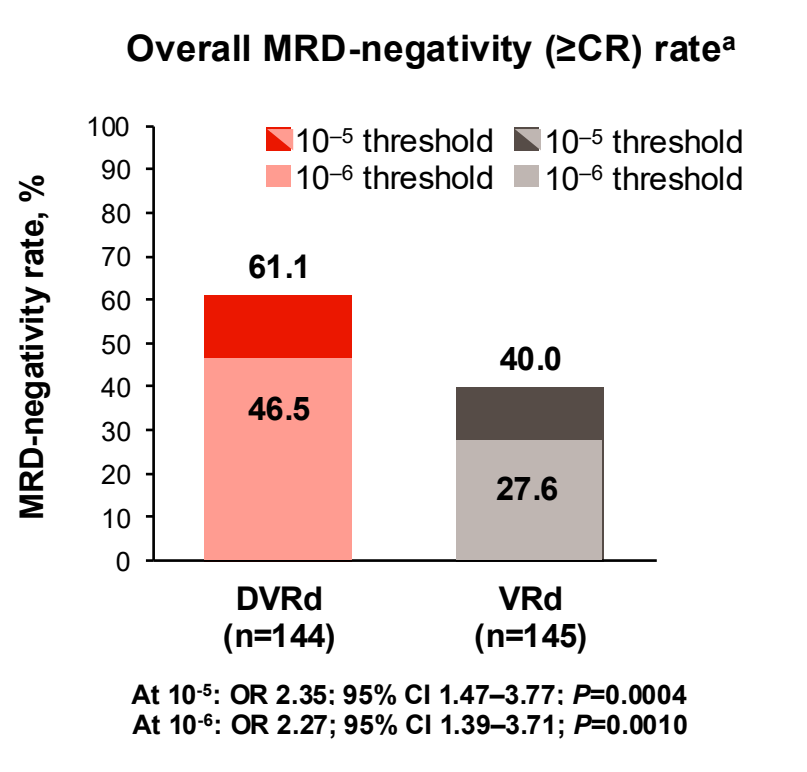

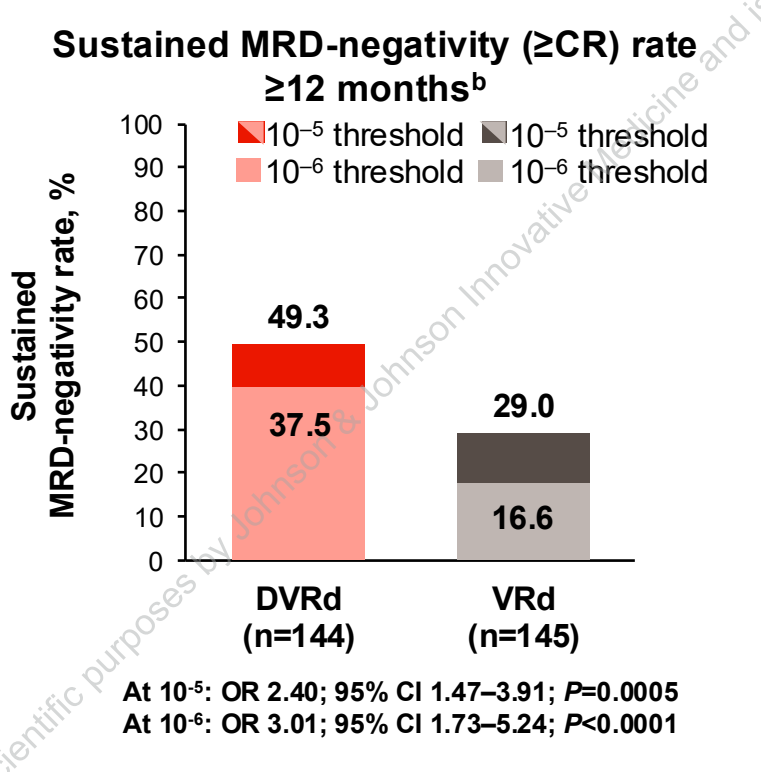

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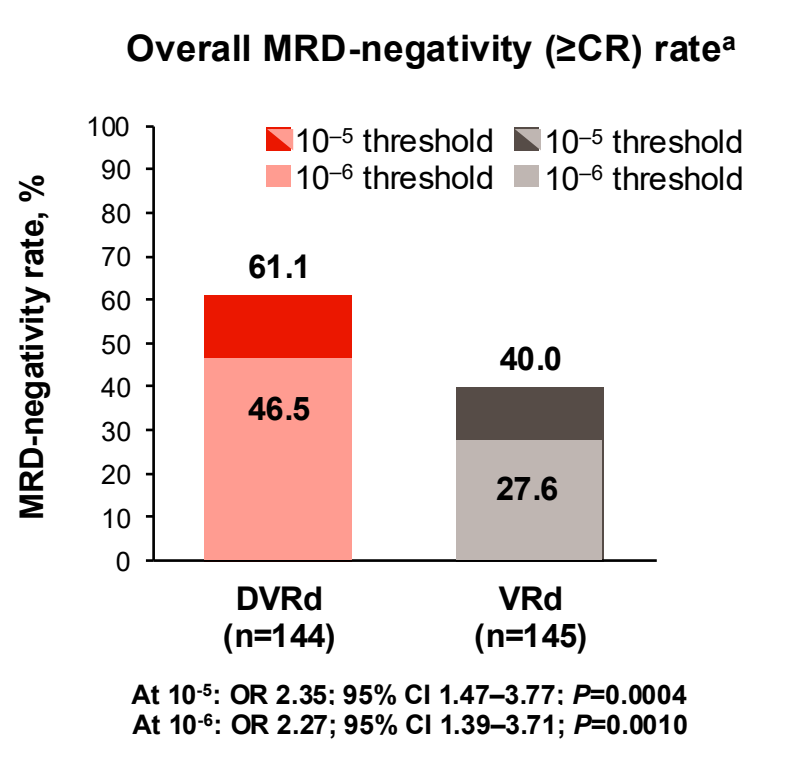
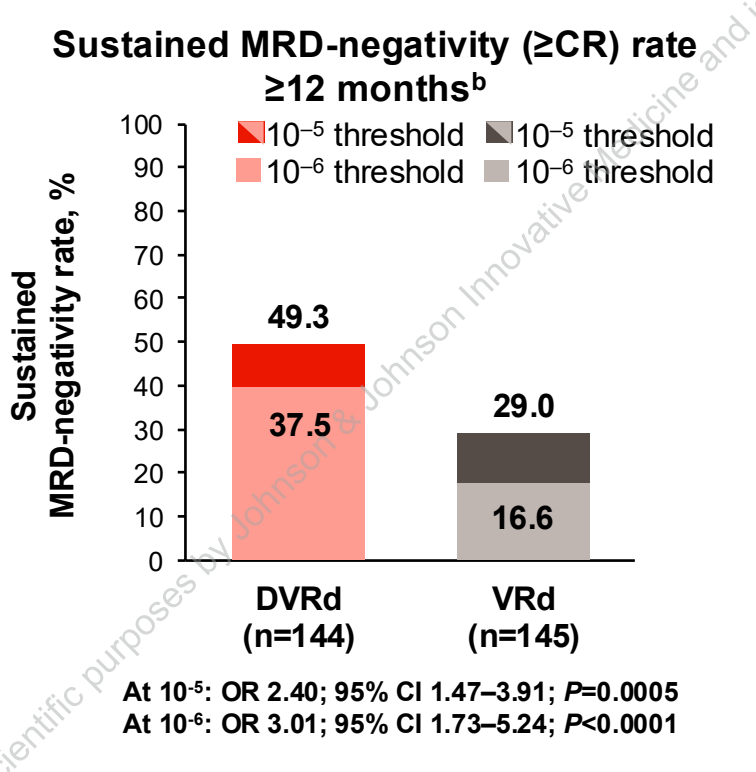
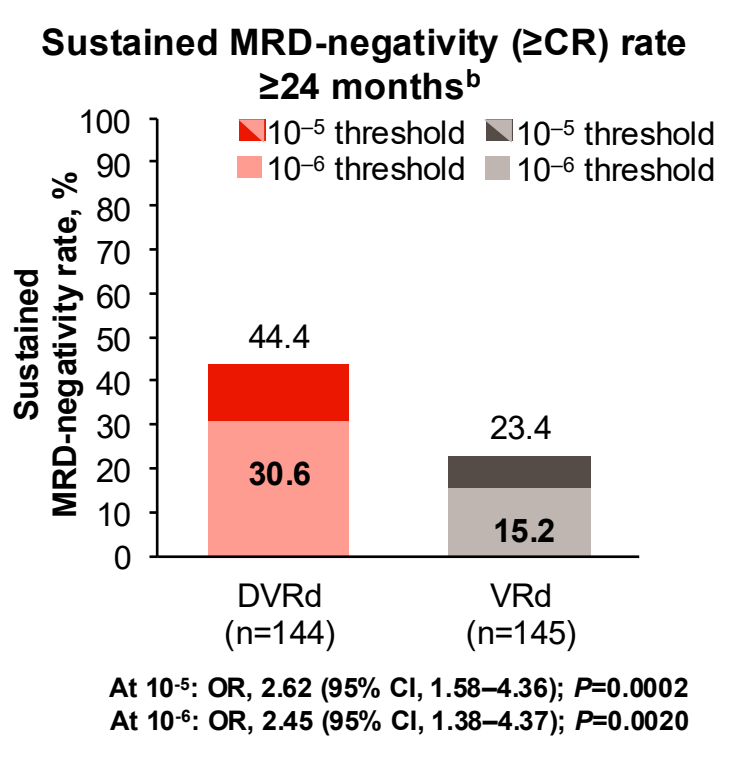
CEPHEUS TIE Final Analysis: Overall and Sustained MRD-Negativity ≥CR Rates







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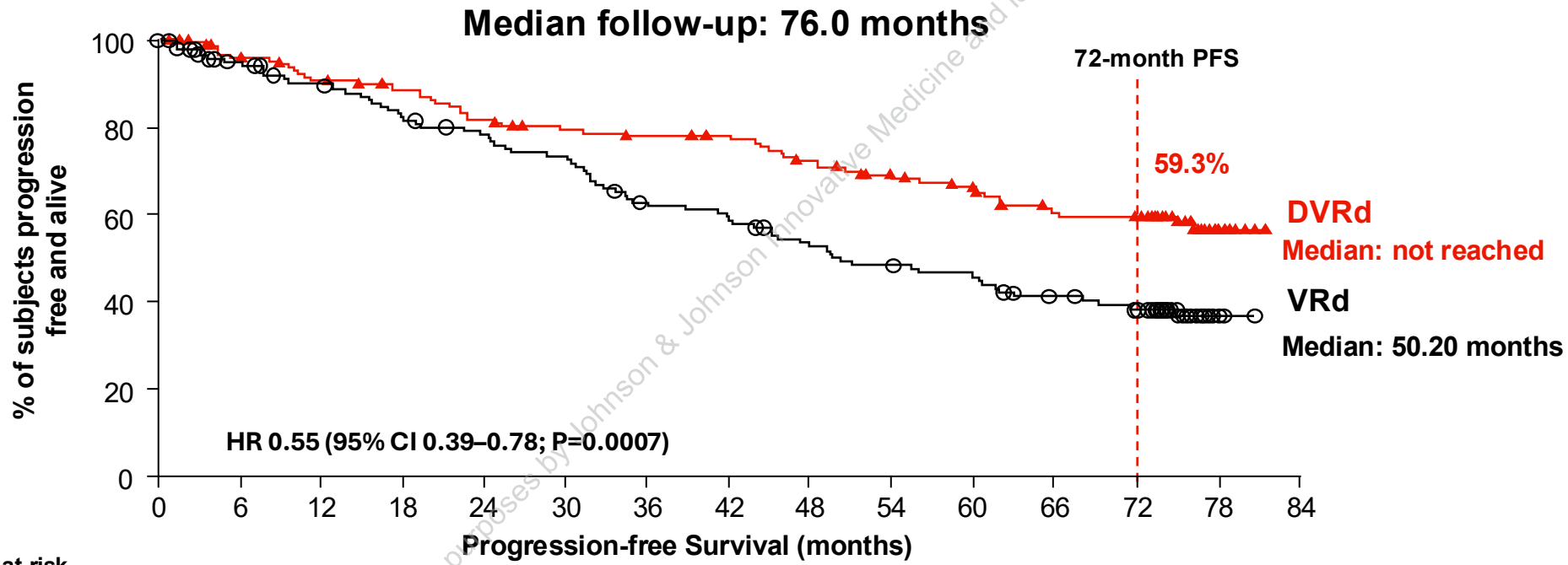
CEPHEUS TIE Final Analysis: Progression-Free Survival

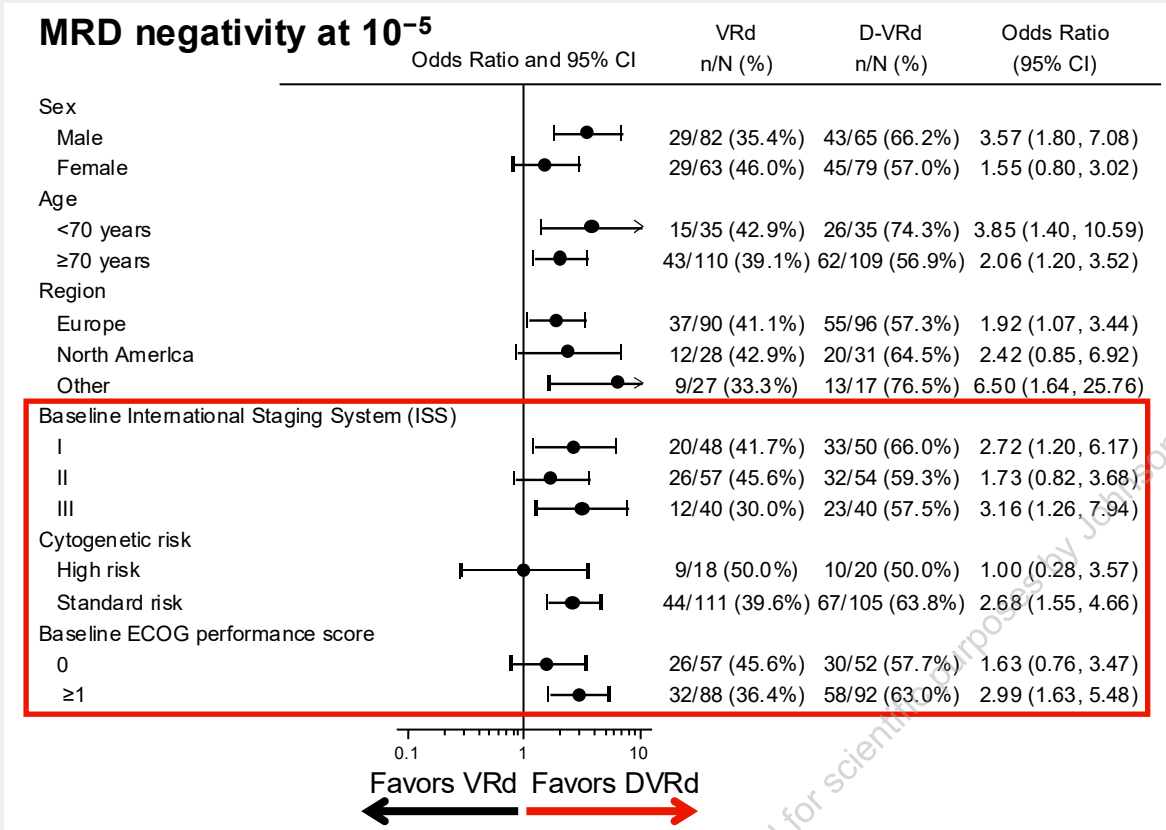


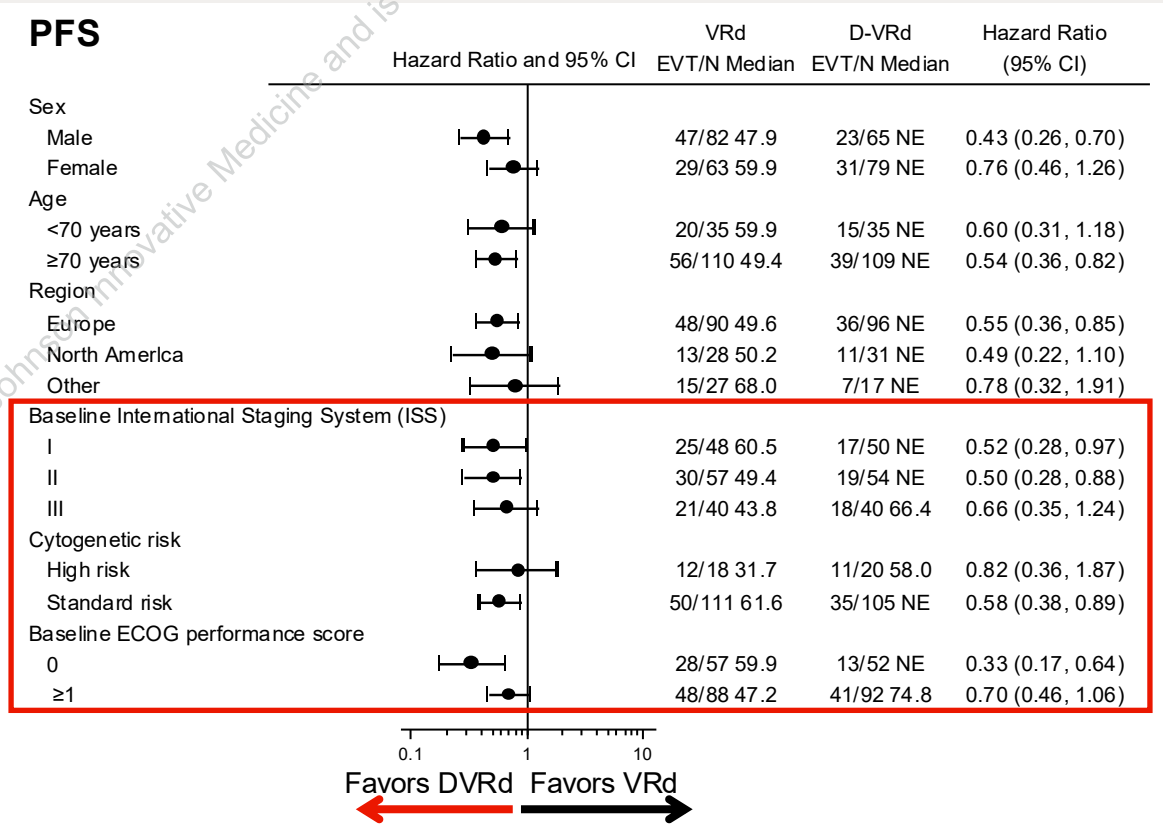
DVRd significantly improved PFS with 45% reduction in risk of disease progression or death vs VRd

DVRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Usmani SZ, et al. *Nat Med* 2025. doi: 10.1038/s41591-024-03485-7.

CEPHEUS TIE Final Analysis: Overall MRD Negativity (10^{-5}) With ≥CR and PFS in Prespecified Subgroups





Treatment effect was generally consistent across subgroups

CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; MRD, minimal residual disease; NE, not estimable; PFS, progression-free survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS TIE Final Analysis: Safety

Safety overview

Event, n (%)	DVRd (n=144)	VRd (n=142)
Any TEAE	144 (100.0)	142 (100.0)
Grade 3 and 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)

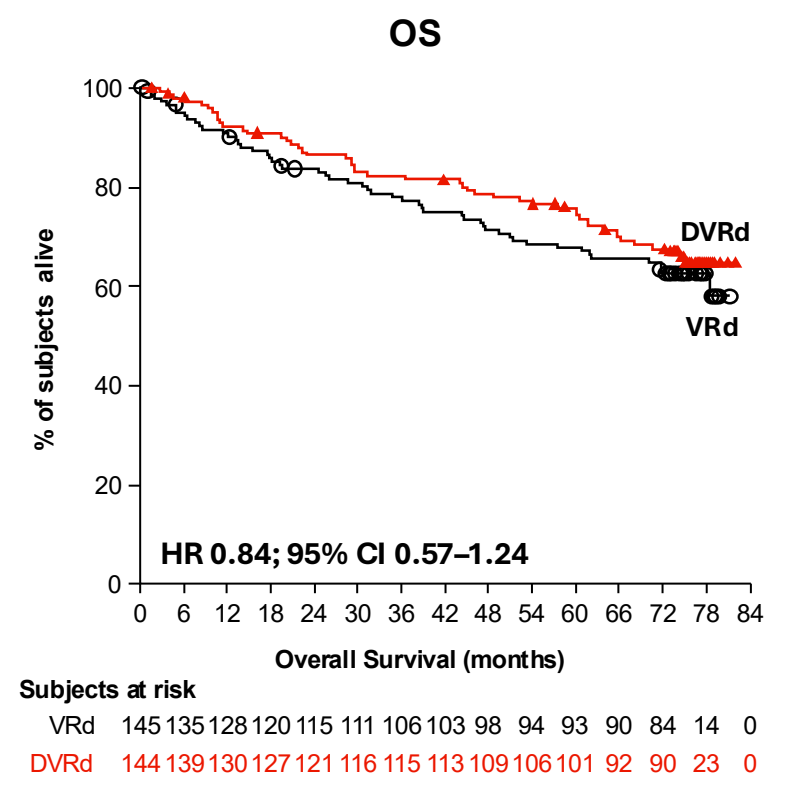
Common (≥5%) grade 3 or 4 TEAEs of interest

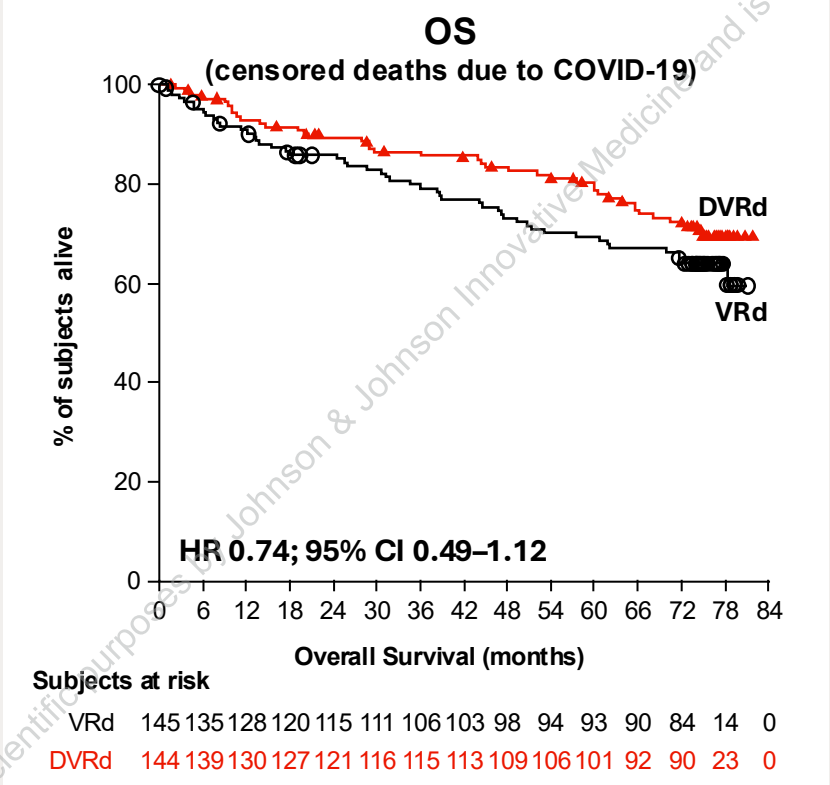
Event, n (%)	DVRd (n=144)	VRd (n=142)
Neutropenia	65 (45.1)	47 (33.1)
Thrombocytopenia	44 (30.6)	33 (23.2)
Anemia	16 (11.1)	14 (9.9)
Diarrhea	20 (13.9)	15 (10.6)
Fatigue	13 (9.0)	15 (10.6)
COVID-19[c]	14 (9.7)	5 (3.5)
Pneumonia	26 (18.1)	19 (13.4)
Peripheral sensory neuropathy	Any Grade: 86 (59.7) Grade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

DVRd showed no additional safety concerns with longer follow-up

[a]Deaths on or within 30 days of treatment. [b]Exposure-adjusted incidence rate: number of subjects 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 subjects without the event. [c]Group term. DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ITT, intent to treat; TEAE, treatment-emergent adverse event; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS TIE Final Analysis: Overall Survival





- Leading cause of death was unrelated AEs:
  - 23 (16.0%) DVRd patients and 15 (10.6%) VRd patients
- Of the total deaths in the TIE population, 11 (3.8%) were COVID-19 related
  - 8/144 (5.6%) DVRd and 3/142 (2.1%) VRd
- Deaths from progressive disease were more than double in the VRd arm
  - 8 (5.6%) DVRd and 17 (12.0%) VRd

OS favored DVRd, especially when censoring for death due to COVID-19 (HR 0.74)
DVRd halved myeloma-related deaths versus VRd

Study was not powered to detect a statistically significant OS difference
AEs, adverse events; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; OS, overall survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS TIE Subgroup: Conclusions

- After a median follow-up of over 6 years, the final analysis of the CEPHEUS trial demonstrated that DVRd continues to show superior efficacy over VRd across key endpoints in TIE patients
- In this post hoc analysis, DVRd improved depth and duration of response:
  - Overall MRD negativity: 61.1% vs 40.0% at 10^{-5}; 46.5% vs 27.6% at 10^{-6}
  - 12-month sustained MRD negativity: 49.3% vs 29.0% at 10^{-5}; 37.5% vs 16.6% at 10^{-6}
  - 24-month sustained MRD negativity: 44.4% vs 23.4% at 10^{-5}; 30.6% vs 15.2% at 10^{-6}
- Risk of disease progression or death was 45% lower for DVRd vs VRd; HR, 0.55
- OS favored DVRd, 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

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

CEPHEUS: NCT03652064. DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.