Dynamic Frailty Analysis of Transplant-Ineligible Patients With NDMM in the Phase 3 MAIA and CEPHEUS Trials of Daratumumab + Lenalidomide-Dexamethasone and Bortezomib-Rd

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Disclosures

COI statement of the presenting author

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Dynamic Frailty Analysis of TIE Patients With NDMM in the Phase 3 MAIA and CEPHEUS Trials: Introduction

Frailty is a well-recognized, high-risk feature and predictor of survival outcomes in patients with MM[1]

- The phase 3 CEPHEUS[2,3] and MAIA[4,5] trials showed addition of daratumumab to VRd or Rd improved outcomes including PFS in non-transplanted patients with NDMM, regardless of baseline frailty

Recent studies suggest that frailty is not a static, but a dynamic state

- Dynamic frailty may be a better predictor of outcomes than a static, one-time frailty measurement[6,7]
- Data on dynamic frailty in phase 2–3 trials are limited *(HOVON 123,[8] HOVON 143,[9,10] IFM 2017-03,[11] DynaFiT,[12] and FiTNEss[13])*, with daratumumab included in three of them
- Understanding both improvements and deteriorations in frailty over a patient's treatment trajectory may have important considerations in treatment delivery

This post hoc subgroup analysis was performed to analyze efficacy and safety outcomes in TIE patients in the phase 3 CEPHEUS and MAIA trials, based on dynamic frailty status

MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Palumbo A, et al. *Blood* 2015;125(13):2068-74. 2. Usmani SZ, et al. *Nat Med* 2025;31(4):1195-202. 3. Zweegman S, et al. *Haematologica* 2025;110(s1):B05. 4. Facon T, et al. *N Engl J Med* 2019;380(22):2104-15. 5. Facon T, et al. *Leukemia* 2025;39(4):942-50. 6. Mian H, et al. *Blood Cancer J* 2023;13(1):76. 7. Smits F, et al. *Blood* 2025;145(5):543-6. 8. Zweegman S, et al. *Blood* 2016;128(22):3305. 9. Stege CAM, et al. *J Clin Oncol* 2021;39(25):2758-67. 10. Groen K, et al. *eClinicalMedicine* 2023;63:102-67. 11. Manier S, et al. *Blood* 2024;144(suppl 1):774. 12. Zhang Y, et al. *J Hematol Oncol* 2024;17(1):48. 13. Cook G, et al. *Blood* 2023;142(suppl 1):4748.

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Post Hoc Dynamic Frailty Analysis of CEPHEUS and MAIA TIE Patients: Methods

- Patients were randomized 1:1 to receive DVRd:VRd (CEPHEUS)[1] or DRd:Rd (MAIA)[2]
- Only TIE patients from CEPHEUS were included in this analysis
- Frailty was retrospectively assessed at baseline and 12, 24, 36, and 48 months
  - IFM simplified frailty score was used:
    - Based on CCI at baseline, present age, and ECOG performance status
    - Nonfrail = score 0/1; frail = score ≥2; ultrafrail = score ≥3
- PFS and overall MRD negativity (MRD-neg 10^{-5} with ≥CR) rates and safety were assessed across dynamic frailty subgroups

CCI, Charlson comorbidity index; CR, complete response; DRd, daratumumab, lenalidomide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; IFM, Intergroupe Francophone du Myélome; MRD, minimal residual disease; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; TIE, transplant ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Usmani SZ, et al. *Nat Med* 2025;31(4):1195-202. 2. Facon T, et al. *N Engl J Med* 2019;380(22):2104-15.

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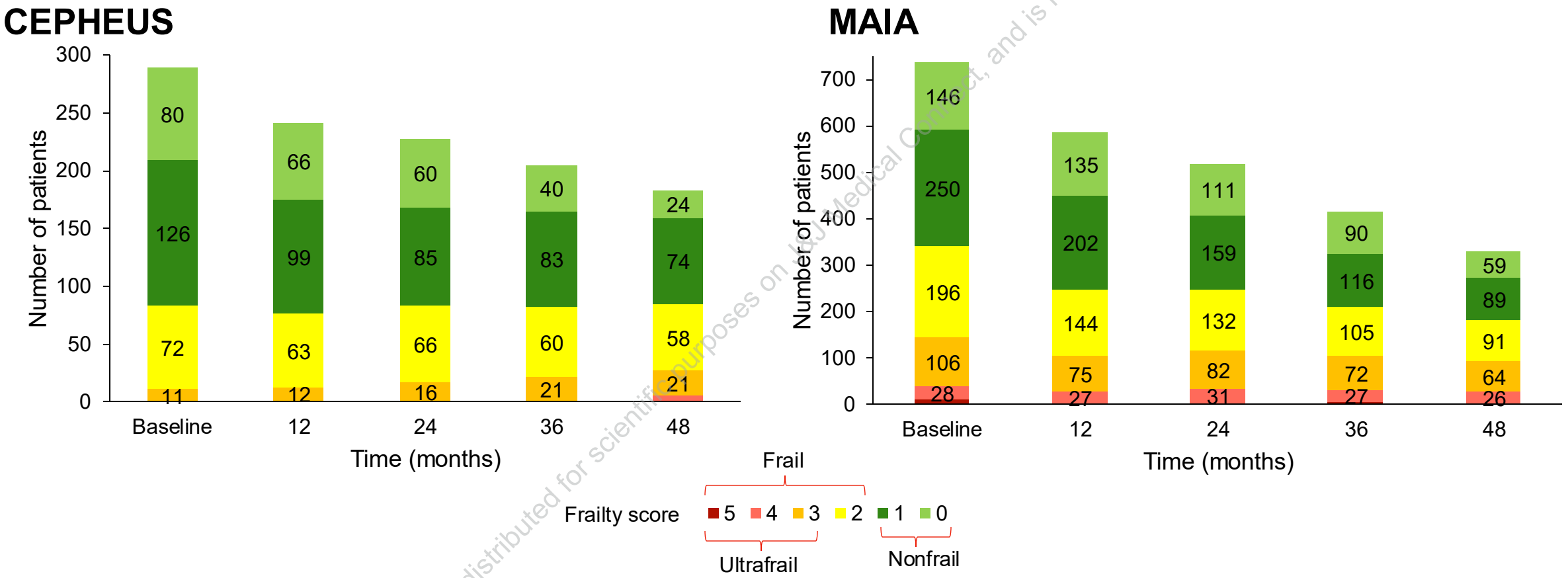
CEPHEUS & MAIA: Distribution of Frailty Scores From Baseline to 48 Months Across Both Treatment Arms



Frailty scores were generally higher in MAIA, including a higher percentage of ultrafrail patients

Frailty Status Over Time per Simplified IFM Criteria for Transplant Ineligible Patients, Intent-to-Treat Analysis Set
IFM, Intergroupe Francophone du Myélome.

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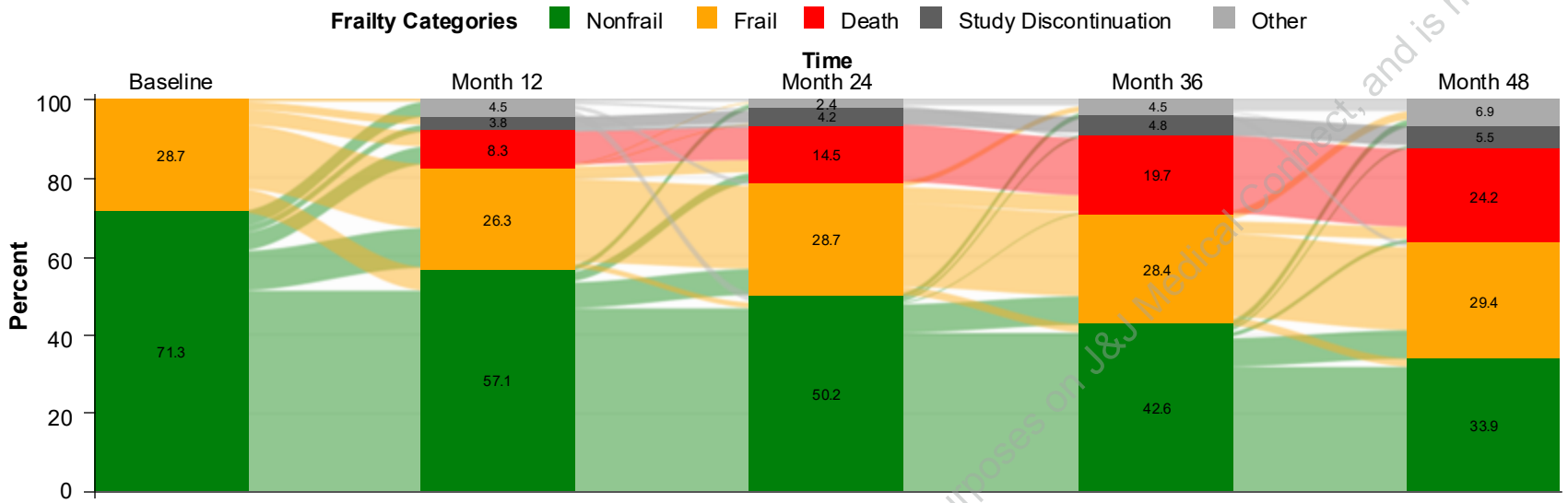
CEPHEUS: Change in Frailty Levels Yearly, Across Both Treatment Arms

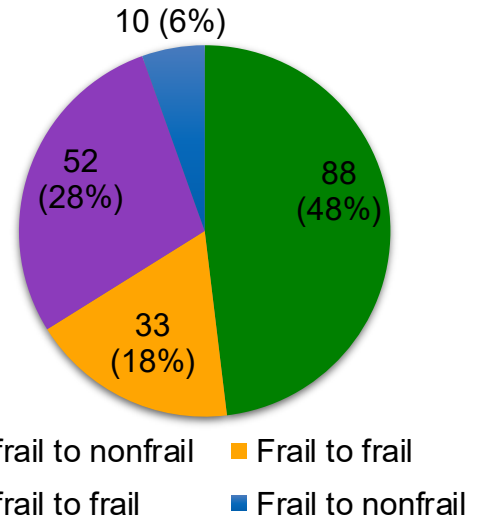


Reasons for deterioration from baseline in 206 patients who were nonfrail at BL, %

Increase in both age and ECOG PS	1.5	3.4	7.3	9.7
Increase in age	2.4	6.8	9.2	11.7
Increase in ECOG PS	10.2	9.7	4.9	3.9

Deterioration of frailty level was due to increases in ECOG and/or age

Shift summary from baseline to 48 months, n (%)



Frailty changed in 34% of patients with data at 48 months

Frailty Status per Simplified IFM Criteria in Year 1 and Beyond for Transplant Ineligible Patients; Intent-to-Treat Analysis Set. 'Other' includes those for whom data for frailty score calculation were not available within the correct time window.
BL, baseline; ECOG PS, Eastern Cooperative Oncology Group performance status; IFM, Intergroupe Francophone du Myélome.

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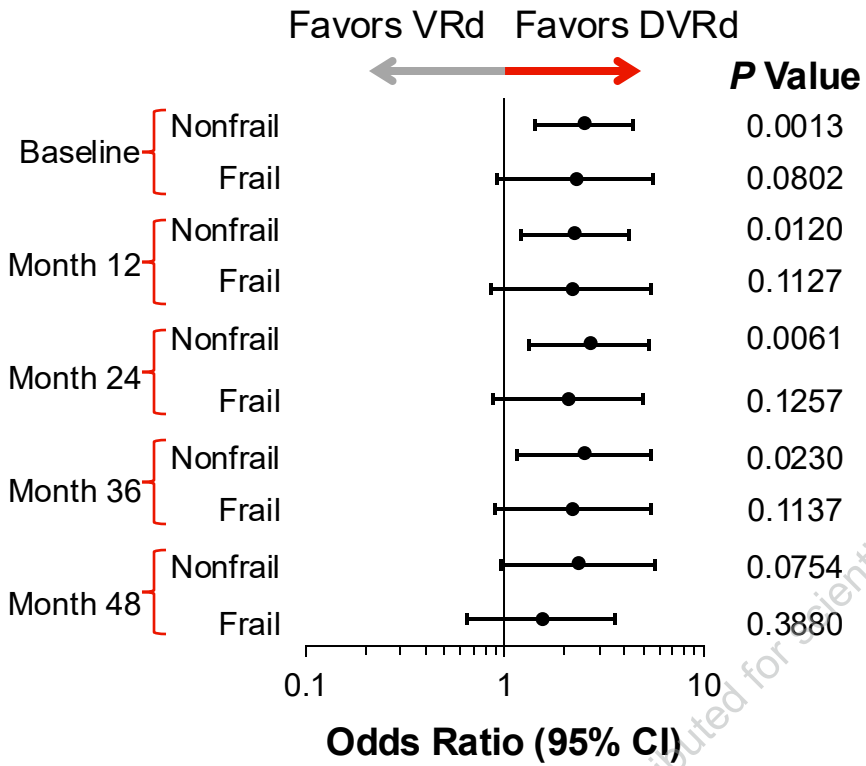
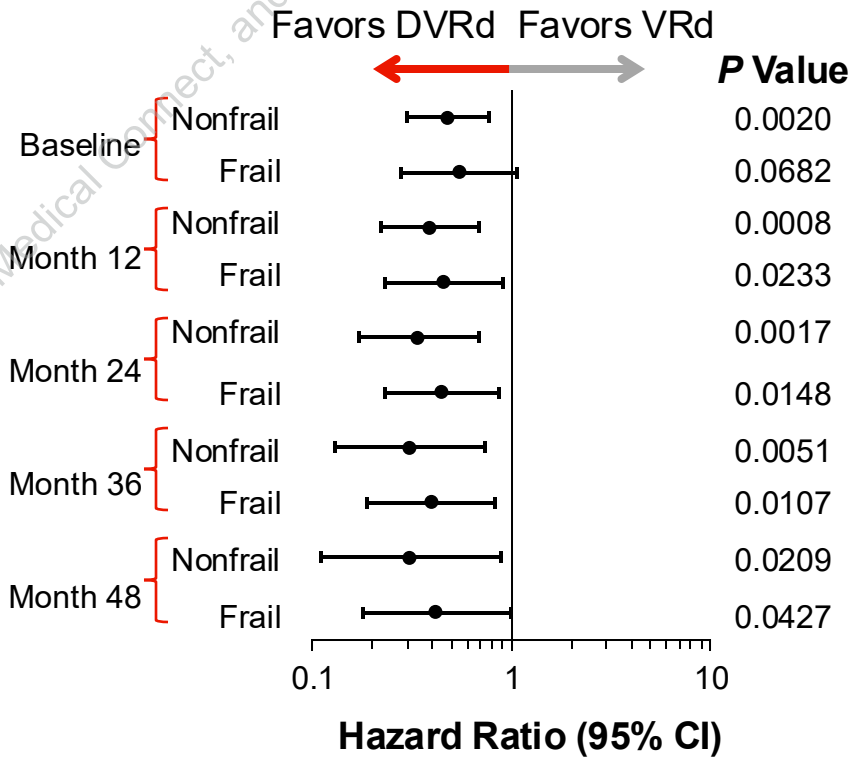
CEPHEUS: MRD[10^{-5}]-negativity ≥CR Rates and PFS Across Frailty Groups Across Timepoints

MRD-neg [10^{-5}] with ≥CR (baseline to 48 months)



PFS (baseline to 48 months)

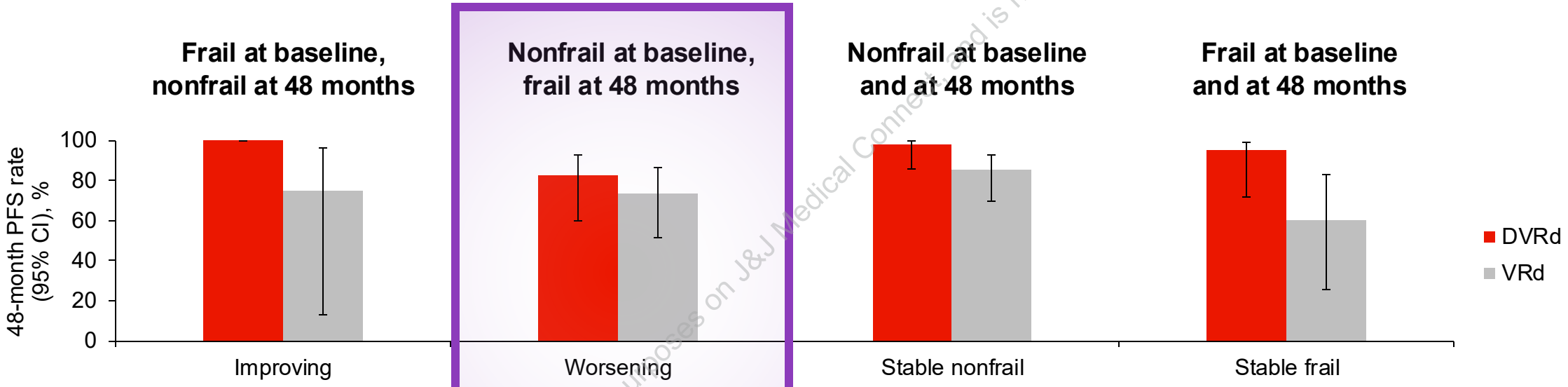


Dara consistently improved MRD-negativity rates across frailty groups and timepoints

PFS was better in the DVRd vs VRd group across frailty groups and timepoints

MRD Negativity Rate at 10^{-5} in Bone Marrow or Progression-Free Survival Based on Computerized Algorithm by Frailty Dynamic Status per Simplified IFM Criteria for Transplant Ineligible Patients; Intent-to-treat Analysis Set
CR, complete response; IFM, Intergroupe Francophone du Myélome; MRD-neg, minimal residual disease negativity;
PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS: Frailty Changes Over 48 Months Influenced PFS



	DVRd n=6	VRd n=4	DVRd n=23	VRd n=29	DVRd n=47	VRd n=41	DVRd n=22	VRd n=11
48-month PFS rate, % (95% CI)	100 (100.0–100.0)	75.0 (12.8–96.1)	82.6 (60.1–93.1)	73.2 (51.8–86.2)	97.9 (85.8–99.7)	85.2 (69.9–93.1)	95.5 (71.9–99.3)	60.0 (25.3–82.7)

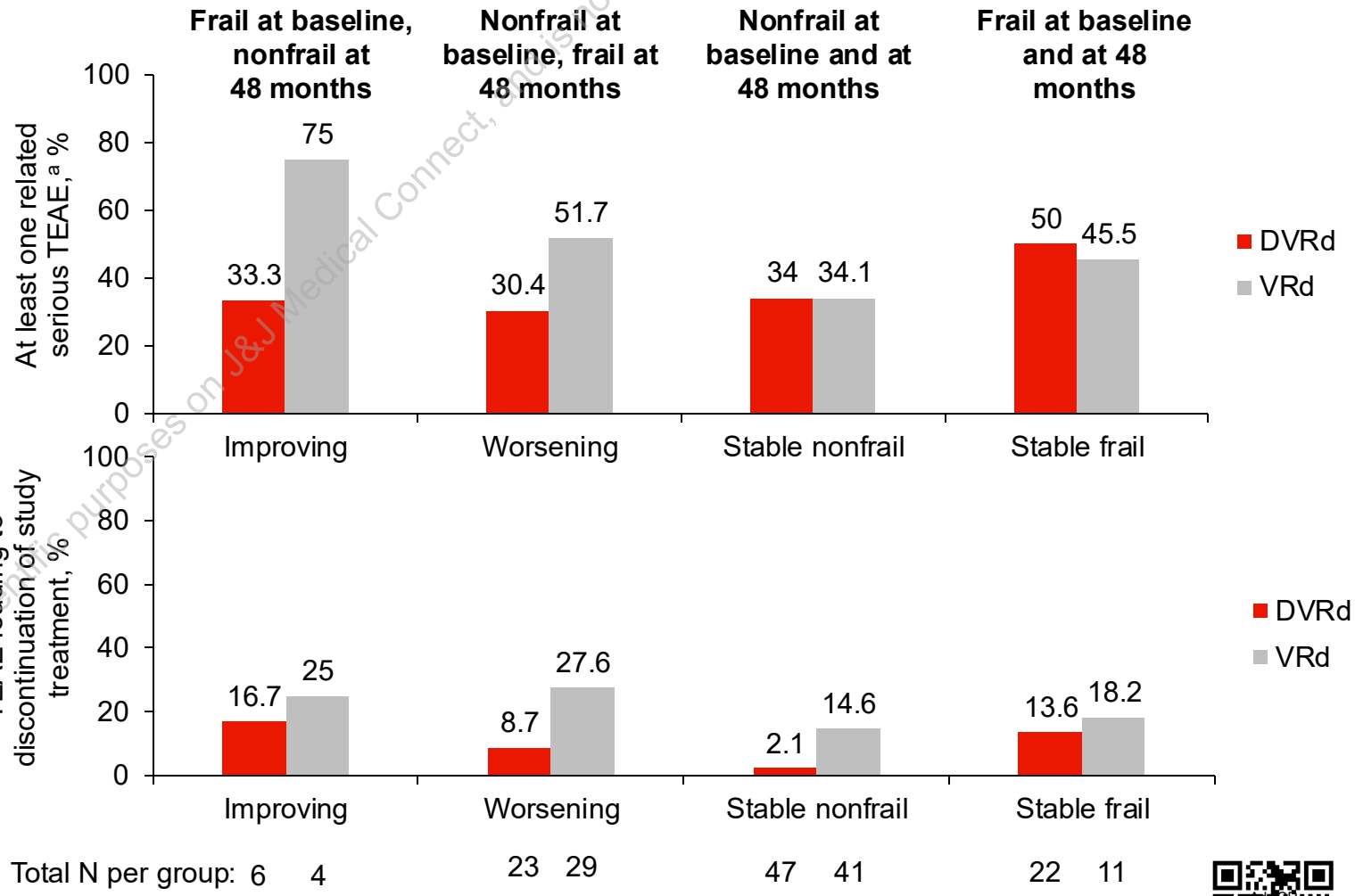
There was a trend towards shorter PFS in those with worsening frailty
Inclusion of Dara is associated with longer PFS regardless of frailty changes

PFS Based on Computerized Algorithm by Frailty Dynamic Status per Simplified IFM Criteria; Intent-to-treat Analysis Set.
Dara, daratumumab; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IFM, Intergroupe Francophone du Myélome; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.

CEPHEUS: Safety Summary Based on Frailty Change at 48 Months

- Incidence of related serious TEAEs was generally similar or lower in patients receiving DVRd vs VRd

- Incidence of TEAEs leading to study treatment discontinuation was generally lower in patients receiving DVRd vs VRd
- Generally, rates of these events were not higher in any of the dynamic frailty subgroups



[a]TEAEs related to at least 1 of the 4 components of study treatment: bortezomib, lenalidomide, dexamethasone, daratumumab. TEAE leading to study treatment discontinuation includes those patients indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
CRF, case report form; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; TEAE, treatment-emergent adverse event; VRd, bortezomib, lenalidomide, and dexamethasone.

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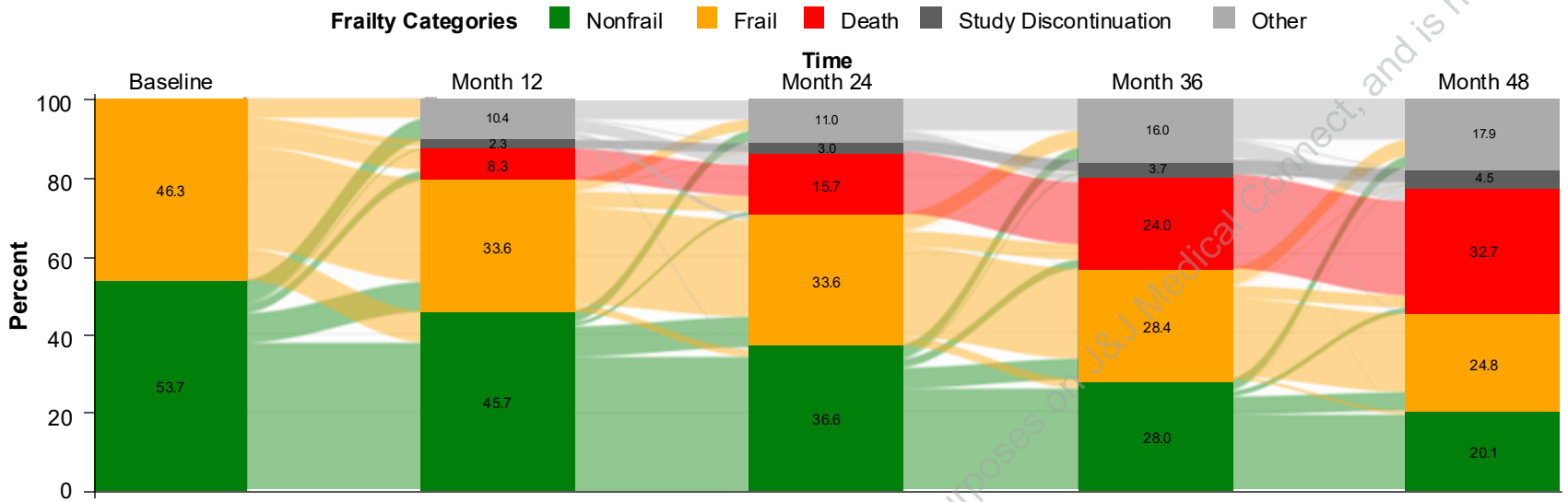
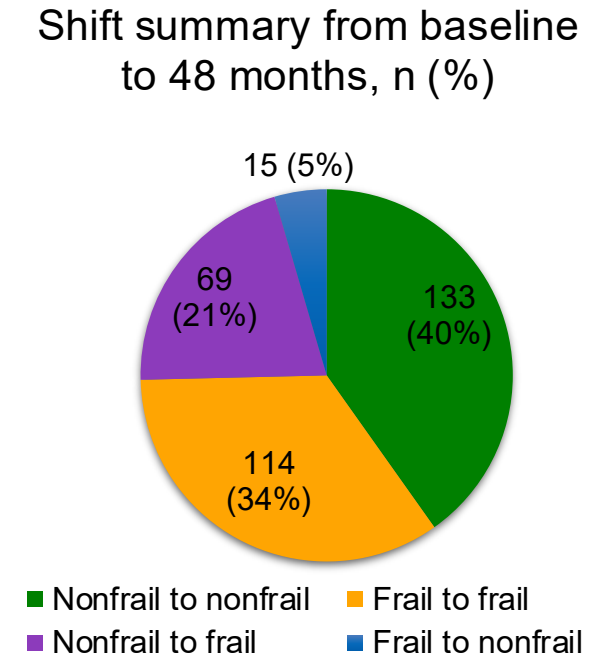
MAIA: Change in Frailty Levels Yearly, Across Both Treatment Arms



Reasons for deterioration from baseline in 396 patients who were nonfrail at BL, %

Increase in both age and ECOG PS	2.0	5.3	7.8	7.3
Increase in age	3.8	6.1	7.3	6.8
Increase in ECOG PS	8.3	8.1	3.8	3.3



Deterioration of frailty level was due to increases in ECOG and/or age

Frailty changed in 26% of patients with data at 48 months

Frailty Status per Simplified IFM Criteria in Year 1 and Beyond; Intent-to-Treat Analysis Set. 'Other' includes those for whom data for frailty score calculation were not available within the correct time window.
BL, baseline; ECOG PS, Eastern Cooperative Oncology Group performance status.

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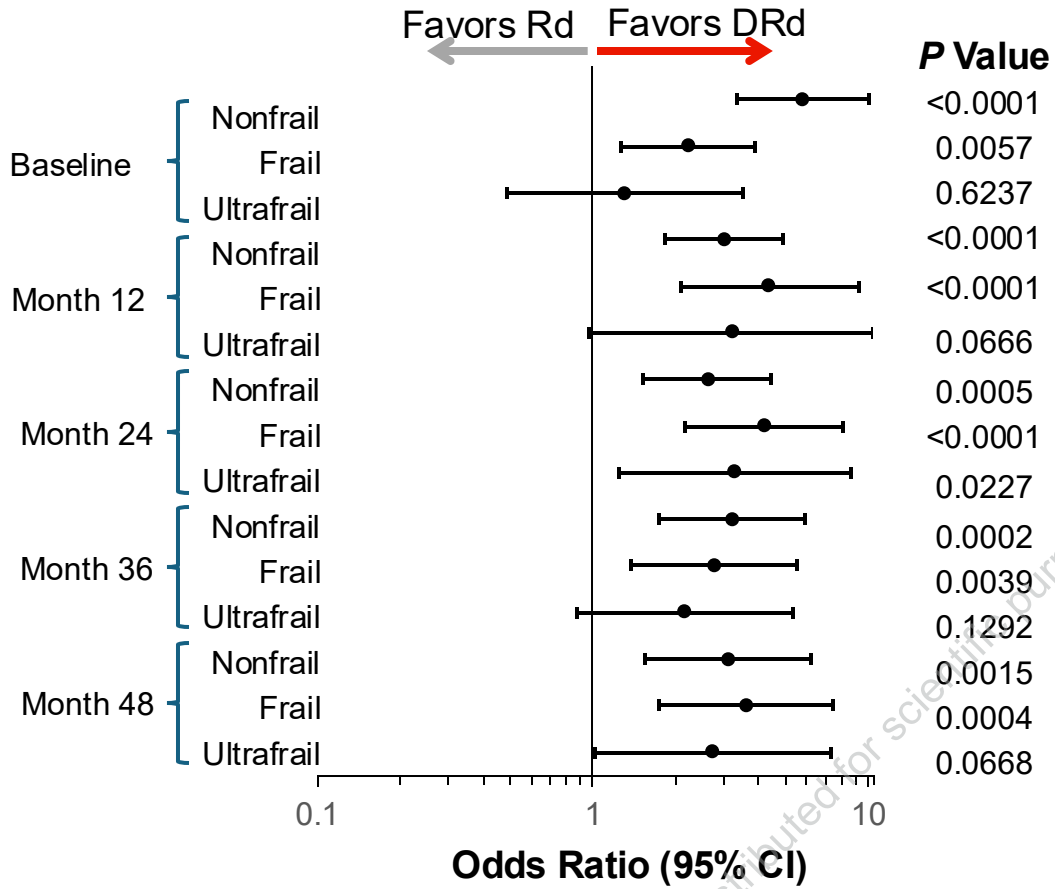
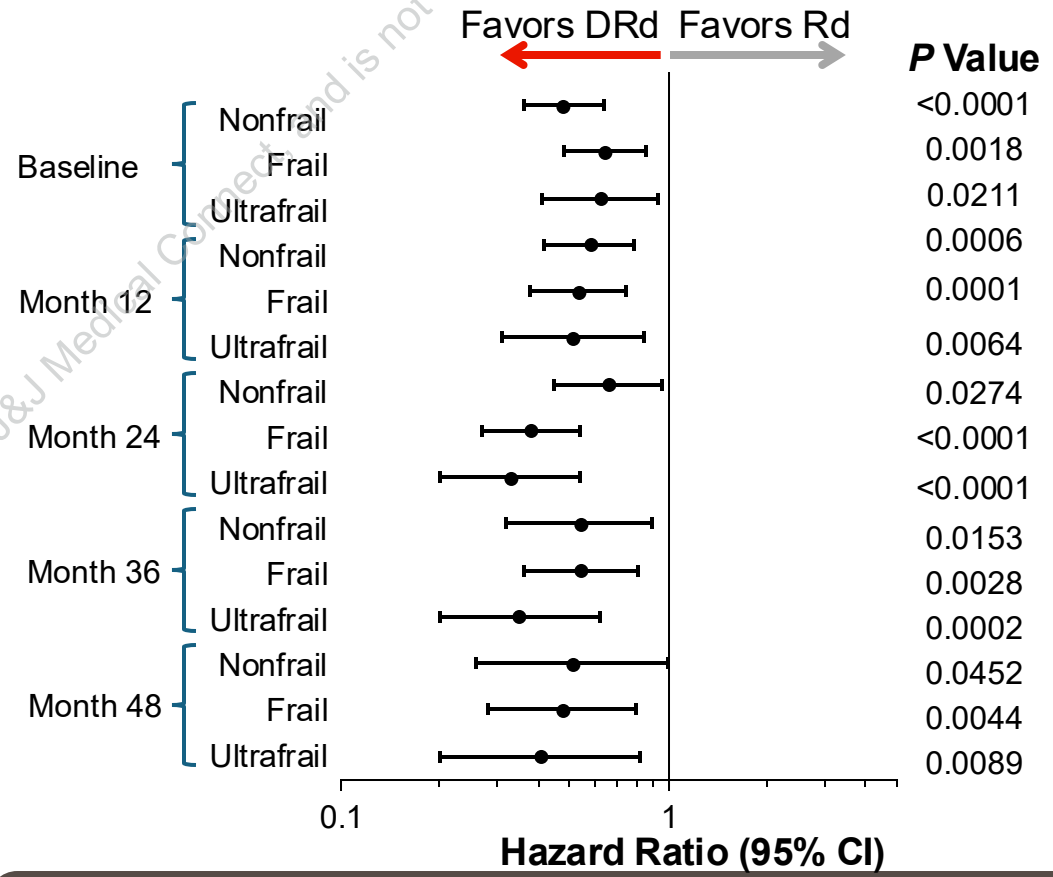
MAIA: MRD [10^{-5}]-negativity ≥CR Rates and PFS Across Frailty Groups, Including Ultrafrail, Across Timepoints



Dara consistently improved MRD-negativity rates across frailty groups and timepoints



Across frailty groups, PFS was better in the DRd vs Rd group across timepoints; Dara provided further PFS benefit in ultrafrail patients across timepoints

MRD Negativity Rate at 10^{-5} in Bone Marrow by Frailty Dynamic Status per Simplified IFM Criteria; Intent-to-treat Analysis Set
Dara, daratumumab; DRd, daratumumab, lenalidomide, and dexamethasone; MRD-neg, minimal residual disease negativity; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

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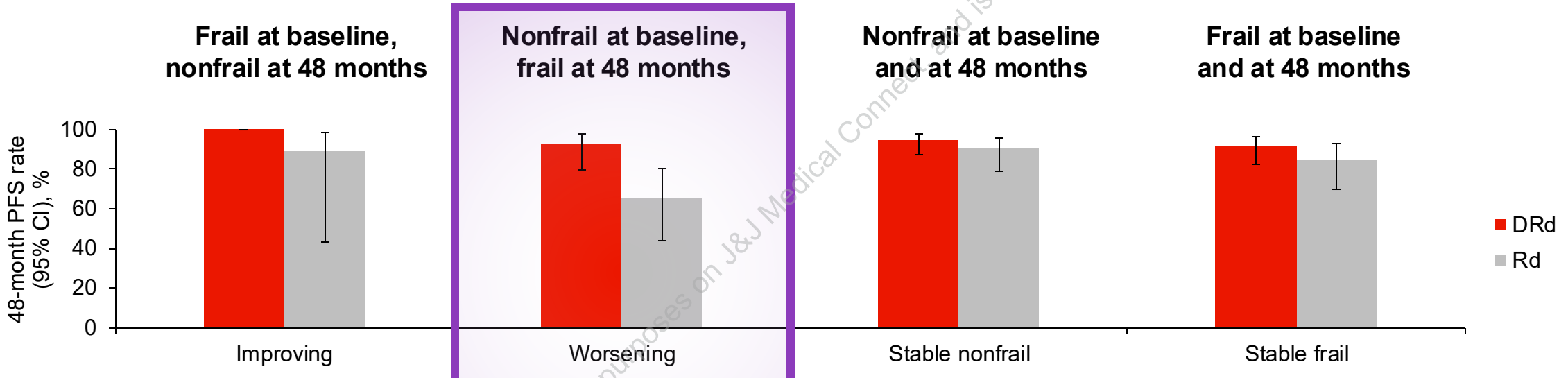
MAIA: Frailty Changes Over 48 Months Influenced PFS



	DRd n=6	Rd n=9	DRd n=43	Rd n=26	DRd n=80	Rd n=53	DRd n=74	Rd n=40
48-month PFS rate, % (95% CI)	100 (100.0–100.0)	88.9 (43.3–98.4)	92.9 (79.5–97.6)	65.4 (44.0–80.3)	95.0 (87.2–98.1)	90.5 (78.6–95.9)	91.8 (82.7–96.2)	85.0 (69.6–93.0)

There was a trend towards shorter PFS in those with worsening frailty
Inclusion of Dara is associated with longer PFS regardless of frailty changes

PFS Based on Computerized Algorithm by Frailty Dynamic Status per Simplified IFM Criteria; Intent-to-treat Analysis Set.
Dara, daratumumab; DRd, daratumumab, lenalidomide, and dexamethasone; IFM, Intergroupe Francophone du Myélome; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

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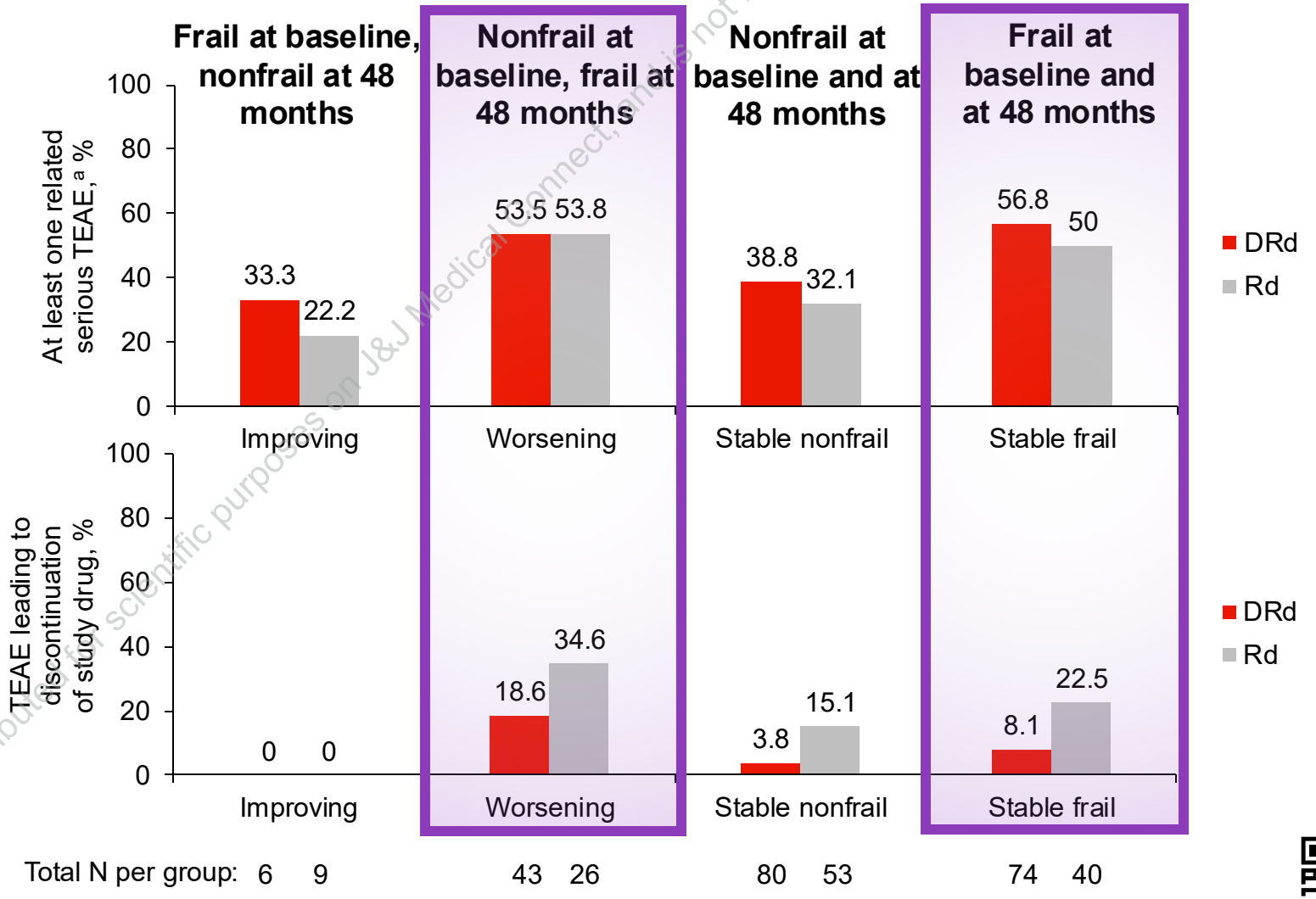
MAIA: Safety Summary Based on Frailty Change at 48 Months

- Incidence of related serious TEAEs was generally similar in patients receiving DRd vs Rd
- Incidence of TEAEs leading to study treatment discontinuation was generally lower in patients receiving DRd vs Rd
- Generally, rates of these events were higher in those with stable frail or worsening frailty



[a]TEAEs related to at least 1 of the 4 components of study treatment: bortezomib, lenalidomide, dexamethasone, daratumumab.
DRd, daratumumab, lenalidomide, and dexamethasone; Rd, lenalidomide, and dexamethasone; TEAE, treatment-emergent adverse event.

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Dynamic Frailty Analysis of TIE Patients With NDMM in the Phase 3 MAIA and CEPHEUS Trials: Conclusions

- **Frailty in some TIE patients with NDMM changed over time in CEPHEUS and MAIA**
  - Most patients had stable frailty, some deteriorated, and a small number improved over 48 months
  - Deterioration of frailty level was due to increases in both ECOG PS and age
- **There was a trend towards shorter PFS in those with worsening frailty**
  - Inclusion of daratumumab is associated with longer PFS regardless of frailty changes
  - Daratumumab consistently improved MRD-negativity rates across frailty groups and timepoints
- **Incidence of related serious TEAEs and TEAEs leading to study treatment discontinuation was generally similar or lower in patients receiving daratumumab vs those not, regardless of changing frailty**
- **Additional data from phase 3 trials investigating the value of treatment adaptation based on dynamic frailty assessments are warranted**

Overall, daratumumab provided a clinical benefit, irrespective of changing frailty status over time

ECOG PS, Eastern Cooperative Oncology Group performance status; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; TEAE; treatment-emergent adverse event; TIE, transplant ineligible.

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https://www.congresshub.com/Oncology/IMS2025/Daratumumab/Mian

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