Age and Frailty Analyses of Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma in the Phase 3 MAIA and CEPHEUS Trials of Daratumumab + Lenalidomide-Dexamethasone and Bortezomib + Lenalidomide-Dexamethasone

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

- The MAIA (NCT02252172) and CEPHEUS (NCT03652064) trials demonstrated that daratumumab (Dara) combined with standard of care (SOC) bortezomib, lenalidomide, and dexamethasone (VRd) or lenalidomide and dexamethasone (Rd) significantly improved clinical outcomes versus SOC in transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM)[1-3]
- Frailty is a well-recognized, high-risk feature and predictor of survival outcomes in patients with multiple myeloma (MM)[4]
- Older patients with MM experience more complicated treatment choices and outcomes due to comorbidities and age-related physiological changes[5]
- In this subgroup analysis, we describe efficacy and safety in TIE patients from both trials by age and baseline frailty using the latest data cuts
  - MAIA: clinical cutoff, Oct 2021; median follow-up, 64.5 months
  - CEPHEUS: clinical cutoff, Oct 2025; median follow-up, 76.0 months

1. Facon T, et al. *N Engl J Med* 2019; 380:2104-15. 2. Facon T, et al. *Leukemia* 2025;39:942-5050. 3. Usmani SZ, et al. *Nature Med* 2025;31:1195-1202. 4. Palumbo A, et al. *Blood* 2015;125(13):2068-74.
5. Côté J, et al. *Front Oncol*. 2026;16:1632275.
Dara, daratumumab; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; SOC, standard of care; TIE, transplant ineligible.

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

- Subgroups included:
  - Age
    - <70 years
    - 70–<75 years
    - ≥75 years
  - Frailty (assessed using the IFM simplified frailty score at baseline)[1]
    - Nonfrail = score of 0/1
    - Frail = score ≥2

- MAIA (N=737; DRd, n=368; Rd, n=369)
  - Median age, 73 years (range, 45-90)
    - <70 years: 155 (21%) patients
    - 70–<75 years: 261 (35%) patients
    - ≥75 years: 321 (44%) patients
  - 341 (46%) patients were frail, 88.0% of whom were ≥70 years
- CEPHEUS (n=289 [TIE]; DVRd, n=144; VRd, n=145)
  - Median age, 72 years (range, 51–80)
    - <70 years: 70 (24%) patients
    - 70–<75 years: 133 (46%) patients
    - ≥75 years: 86 (30%) patients
  - 83 (29%) patients were frail, 86.0% of whom were ≥70 years

1. Facon T, et al *Leukemia* 2020; 34:224-33.

IFM, Intergroup Francophone Myeloma; NDMM, newly diagnosed multiple myeloma; TIE, transplant ineligible.

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MAIA & CEPHEUS: Patient Population

- Median treatment duration was up to 2 to 3 times longer in those receiving Dara-based regimens across age and frailty subgroups in both MAIA and CEPHEUS
  - Within treatment arms, treatment duration was longer in nonfrail patients, and also generally longer in younger patients

Overall		Frail		Nonfrail		<70 years		70–<75 years		≥75 years	
MAIA											
DRd (n=364)	**Rd (n=365)**	**DRd (n=168)**	**Rd (n=166)**	**DRd (n=196)**	**Rd (n=199)**	**DRd (n=78)**	**Rd (n=76)**	**DRd (n=129)**	**Rd (n=130)**	**DRd (n=157)**	**Rd (n=159)**
47.5 (0.1–77.3)	22.6 (0.0–77.5)	39.1 (0.1–77.3)	20.7 (0.0–69.3)	54.6 (0.7–76.2)	25.8 (0.3–77.5)	59.5 (0.1–73.3)	21.0 (0.0–76.3)	49.2 (0.2–76.2)	25.9 (0.0–77.5)	40.8 (0.2–77.3)	20.1 (0.1–71.4)
CEPHEUS											
DVRd (n=144)	**VRd (n=142)**	**DVRd (n=48)**	**VRd (n=33)**	**DVRd (n=96)**	**VRd (n=109)**	**DVRd (n=35)**	**VRd (n=35)**	**DVRd (n=68)**	**VRd (n=65)**	**DVRd (n=41)**	**VRd (n=42)**
57.1 (0.1–81.9)	34.0 (0.5–81.0)	44.5 (0.5–80.7)	25.7 (0.5–79.4)	62.6 (0.1–81.9)	35.4 (0.5–81.0)	72.5 (3.6–78.8)	38.9 (0.5–81.0)	55.3 (0.1–81.9)	33.6 (1.2–79.9)	49.9 (2.1–80.7)	23.1 (0.5–78.9)

Dara, daratumumab; DRd, daratumumab + lenalidomide-dexamethasone; DVRd, daratumumab and bortezomib + lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; TIE, transplant-ineligible; VRd, bortezomib + lenalidomide-dexamethasone; y, years.

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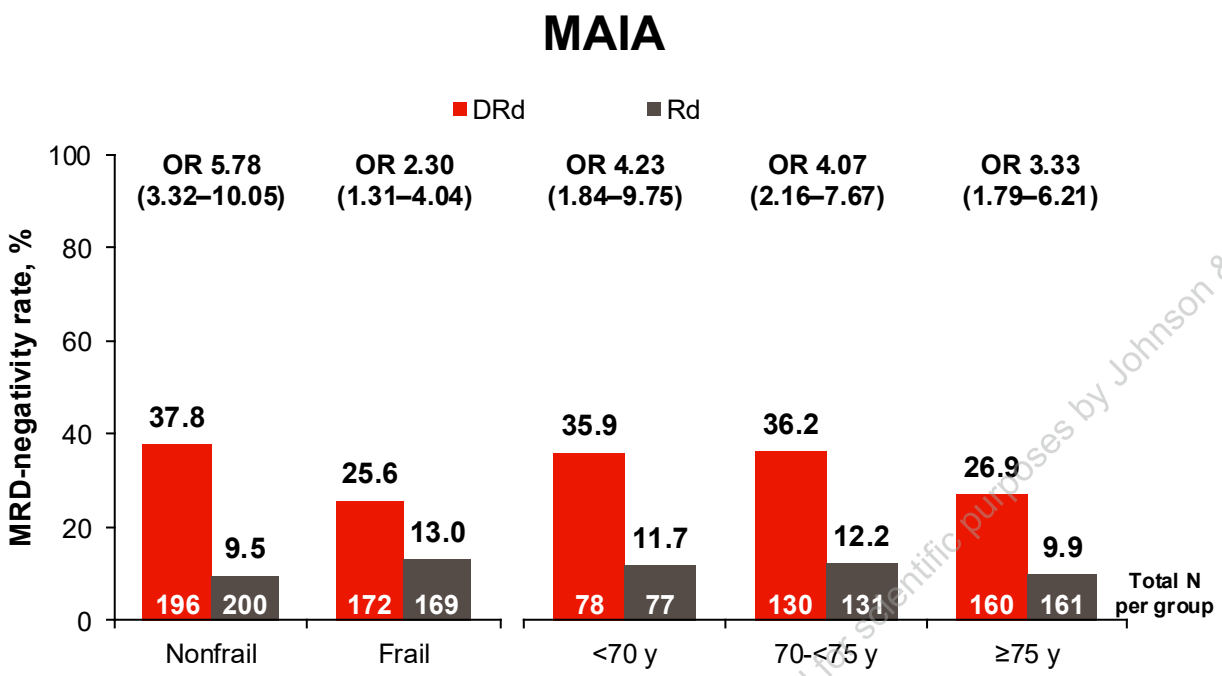
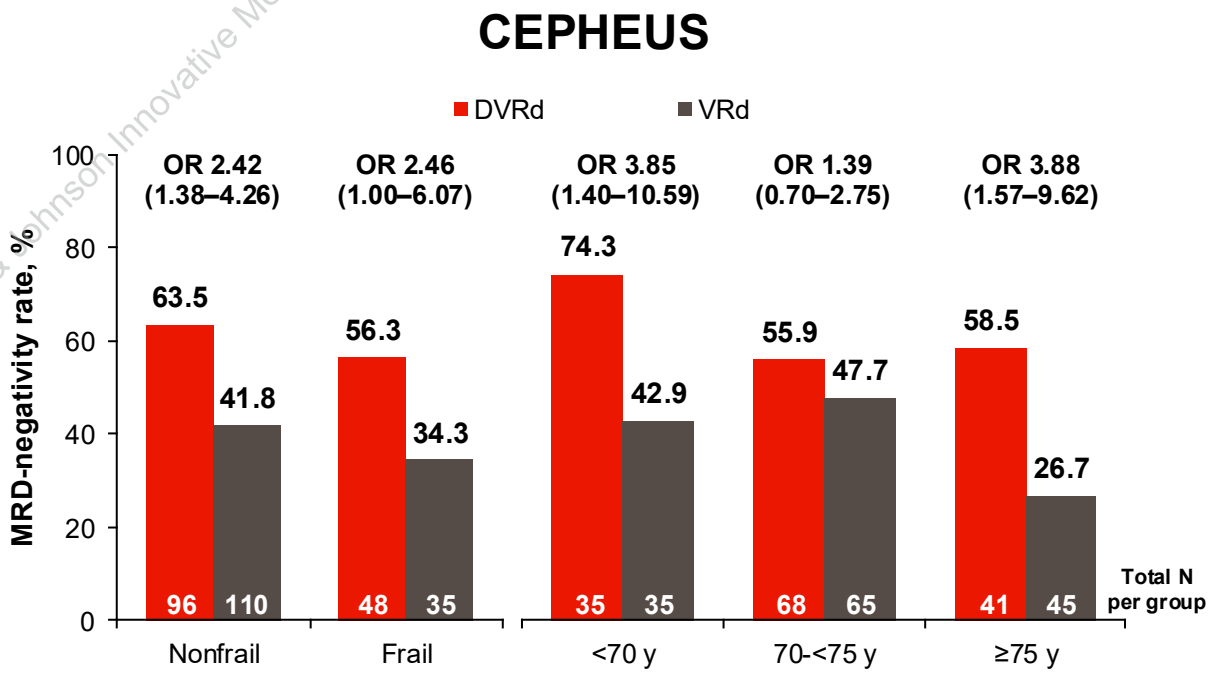
MAIA & CEPHEUS: Overall MRD-Negativity (10^{-5}) ≥CR Rates Were Consistently Improved

- DRd or DVRd consistently improved overall MRD negativity in both MAIA and CEPHEUS





≥CR, complete response or better; DRd, daratumumab + lenalidomide-dexamethasone; DVRd, daratumumab and bortezomib + lenalidomide-dexamethasone; MRD, minimal residual disease; OR, odds ratio; Rd, lenalidomide-dexamethasone; VRd, bortezomib + lenalidomide-dexamethasone; y, years.

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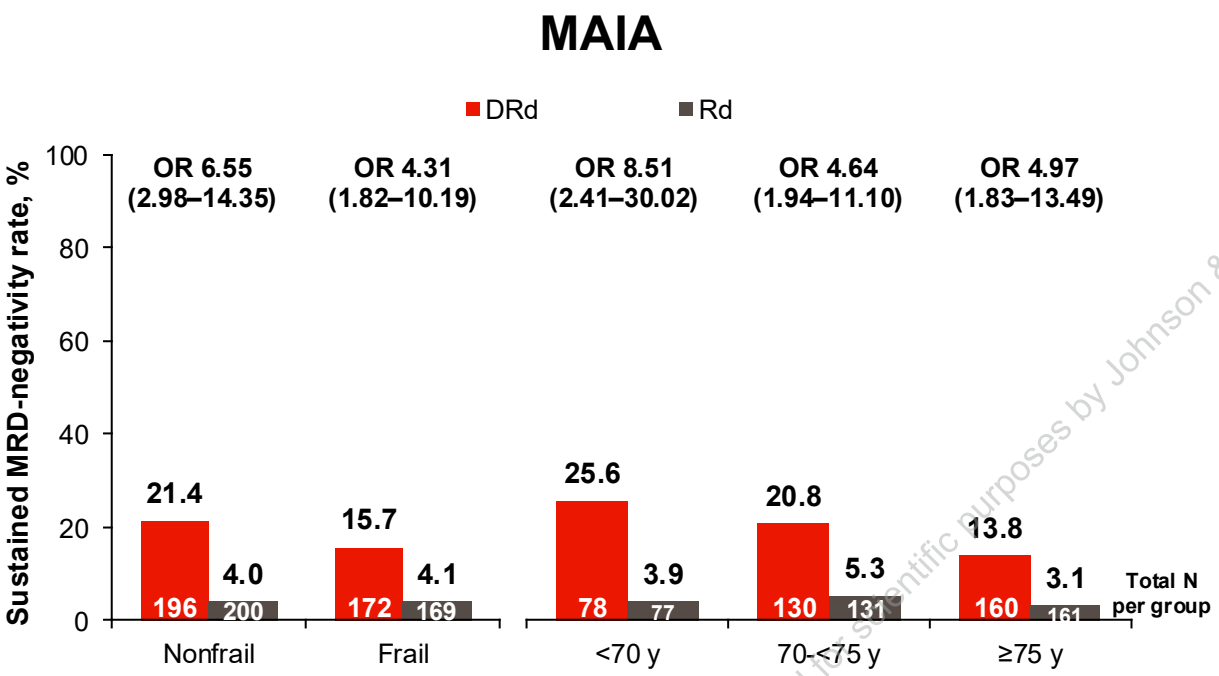
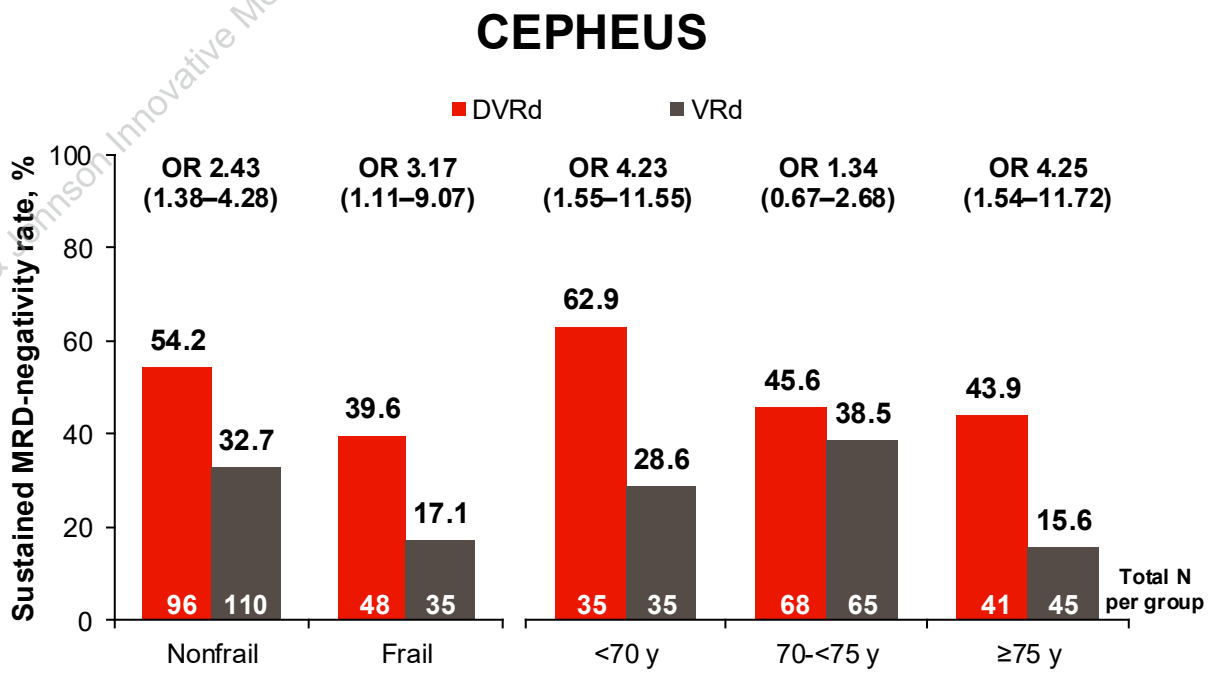
MAIA & CEPHEUS: Sustained MRD-Negativity (10^{-5}) ≥CR Rates Were Consistently Improved

- DRd or DVRd consistently improved sustained MRD negativity in both MAIA and CEPHEUS





≥CR, complete response or better; DRd, daratumumab + lenalidomide-dexamethasone; DVRd, daratumumab and bortezomib + lenalidomide-dexamethasone; MRD, minimal residual disease; OR, odds ratio; Rd, lenalidomide-dexamethasone; VRd, bortezomib + lenalidomide-dexamethasone; y, years.

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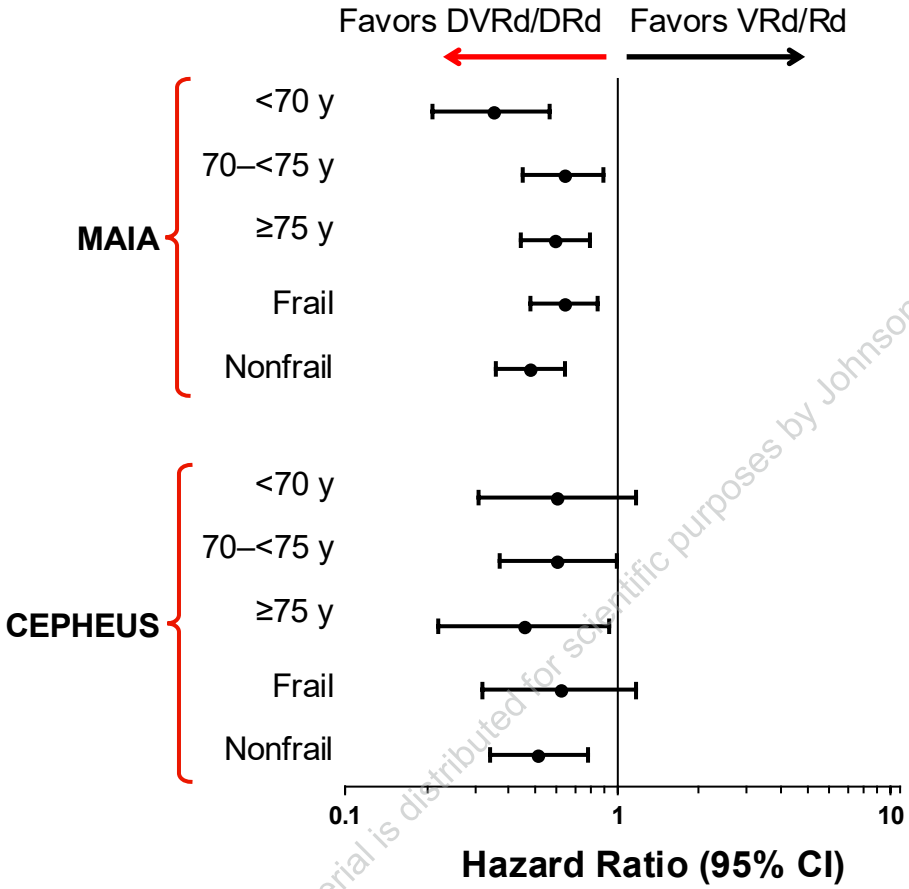
MAIA & CEPHEUS: PFS Was Improved Across Most Age and Frailty Subgroups

- Dara improved PFS in MAIA and CEPHEUS patients across most age and frailty subgroups



	DVRd/DRd median, months (95% CI)	VRd/Rd median, months (95% CI)	HR (95% CI)
MAIA <70 y	NE (62.13, NE)	39.16 (23.03, 51.15)	0.35 (0.21, 0.56)
MAIA 70–<75 y	61.93 (48.39, NE)	37.52 (26.94, 46.23)	0.64 (0.45, 0.89)
MAIA ≥75 y	54.31 (39.20, 61.86)	31.38 (23.59, 37.78)	0.59 (0.44, 0.79)
MAIA Frail	52.17 (39.13, 61.86)	30.39 (22.41, 35.42)	0.64 (0.48, 0.85)
MAIA Nonfrail	73.72 (61.67, NE)	37.78 (31.24, 45.21)	0.48 (0.36, 0.64)
CEPHEUS <70 y	NE (56.02, NE)	59.89 (38.74, NE)	0.60 (0.31, 1.18)
CEPHEUS 70–<75 y	NE (60.29, NE)	51.09 (32.72, 71.39)	0.60 (0.37, 0.99)
CEPHEUS ≥75 y	NE (76.09, NE)	45.14 (31.41, NE)	0.46 (0.22, 0.94)
CEPHEUS Frail	76.09 (43.93, NE)	38.74 (24.38, NE)	0.62 (0.32, 1.18)
CEPHEUS Nonfrail	NE (74.81, NE)	55.95 (45.14, 71.39)	0.51 (0.34, 0.78)

CI, confidence interval; Dara, daratumumab; DRd, daratumumab + lenalidomide-dexamethasone; DVRd, daratumumab and bortezomib + lenalidomide-dexamethasone; NE, not estimated; PFS, progression-free survival; Rd, lenalidomide-dexamethasone; TIE, transplant-ineligible; VRd, bortezomib + lenalidomide-dexamethasone; y, year.

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MAIA & CEPHEUS: Common Grade 3/4 TEAEs of Interest and Treatment-Related Discontinuations

- In MAIA, rates of grade 3/4 TEAEs were generally higher in frail vs nonfrail patients, and in older vs younger patients within treatment arms
- In CEPHEUS, there were no apparent trends in the incidence of grade 3/4 TEAEs, including COVID-19, based on age or frailty
- The incidence of TEAEs leading to study treatment discontinuation was slightly lower in those receiving Dara across age and frailty subgroups in MAIA and CEPHEUS

	Frail		Nonfrail		<70 years		70–<75 years		≥75 years	
MAIA	**DRd (n=168)**	**Rd (n=166)**	**DRd (n=196)**	**Rd (n=199)**	**DRd (n=78)**	**Rd (n=76)**	**DRd (n=129)**	**Rd (n=130)**	**DRd (n=157)**	**Rd (n=159)**
Any grade 3/4 TEAE	161 (95.8)	152 (91.6)	188 (95.9)	172 (86.4)	72 (92.3)	62 (81.6)	127 (98.4)	111 (85.4)	150 (95.5)	151 (95.0)
Neutropenia	101 (60.1)	56 (33.7)	96 (49.0)	79 (39.7)	37 (47.4)	21 (27.6)	62 (48.1)	48 (36.9)	98 (62.4)	66 (41.5)
Infections & infestations SOC[a]	78 (46.4)	53 (31.9)	77 (39.3)	55 (27.6)	29 (37.2)	19 (25.0)	58 (45.0)	36 (27.7)	68 (43.3)	53 (33.3)
TEAE leading to study treatment discontinuation	27 (16.1)	40 (24.1)	26 (13.3)	47 (23.6)	9 (11.5)	11 (14.5)	20 (15.5)	32 (24.6)	24 (15.3)	44 (27.7)

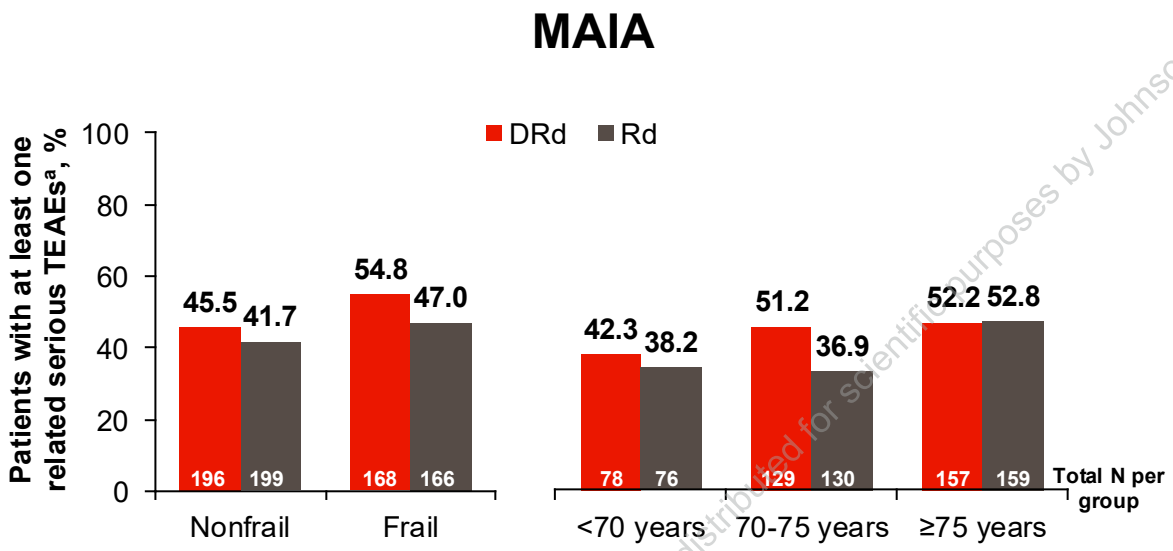
CEPHEUS	**DVRd (n=48)**	**VRd (n=33)**	**DVRd (n=96)**	**VRd (n=109)**	**DVRd (n=35)**	**VRd (n=35)**	**DVRd (n=68)**	**VRd (n=65)**	**DVRd (n=41)**	**VRd (n=42)**
Any grade 3/4 TEAE	48 (100)	29 (87.9)	87 (90.6)	97 (89.0)	32 (91.4)	30 (85.7)	62 (91.2)	58 (89.2)	41 (100)	38 (90.5)
Neutropenia	23 (47.9)	11 (33.3)	42 (43.8)	36 (33.0)	15 (42.9)	12 (34.3)	26 (38.2)	24 (36.9)	24 (58.5)	11 (26.2)
Infections & infestations SOC[b]	22 (45.8)	14 (42.4)	41 (42.7)	33 (30.3)	12 (34.3)	15 (42.9)	34 (50.0)	17 (26.2)	17 (41.5)	15 (35.7)
TEAE leading to study treatment discontinuation	5 (10.4)	7 (21.2)	9 (9.4)	26 (23.9)	2 (5.7)	7 (20.0)	7 (10.3)	12 (18.5)	5 (12.2)	14 (33.3)

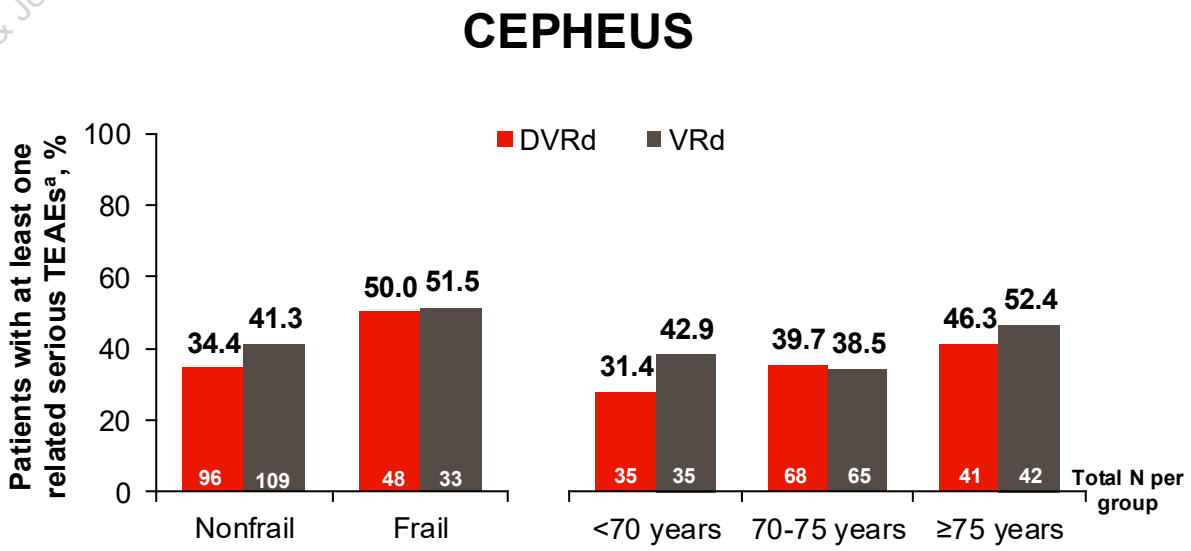
[a]In MAIA, COVID-19 infections/pneumonia were reported in <2% of patients in the DRd arm across subgroups
[b]In CEPHEUS, COVID-19 infections were reported in frail (DVRd, n=6; VRd, n=0), nonfrail (DVRd, n=8; VRd, n=5), <70 y (DVRd, n=3; VRd, n=2), 70-<75 y (DVRd, n=9; VRd, n=2), and ≥75 y (DVRd, n=2; VRd, n=1) subgroups. COVID-19 pneumonia was reported in frail (DVRd, n=1; VRd, n=1), nonfrail (DVRd, n=4; VRd, n=2), <70 y (DVRd, n=0; VRd, n=1), 70-<75 y (DVRd, n=3; VRd, n=1), and ≥75 y (DVRd, n=2; VRd, n=1) subgroups.

COVID-19, Coronavirus disease 2019; Dara, daratumumab; DRd, daratumumab + lenalidomide-dexamethasone; DVRd, daratumumab and bortezomib + lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; SOC, standard of care; TEAE, treatment-emergent adverse event; VRd, bortezomib + lenalidomide-dexamethasone; y, years.

MAIA & CEPHEUS: Similar Incidence of Related Serious TEAEs Among Patients Across Most Age and Frailty Subgroups

- The incidence of related serious TEAEs was similar in those receiving DRd or DVRd compared with Rd or VRd across most age and frailty subgroups in MAIA and CEPHEUS
- In MAIA, a greater percentage of patients died in the Rd vs DRd arm, regardless of frailty, and more patients died of AEs in the frail vs nonfrail subgroup, regardless of treatment. Across age subgroups, more older patients died of progressive disease regardless of treatment





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

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MAIA & CEPHEUS: Causes of Death

- In MAIA, more patients died in the Rd vs DRd arm, regardless of frailty, and more patients died of AEs in the frail vs nonfrail subgroup, regardless of treatment. Across age subgroups, more older patients died of progressive disease regardless of treatment
- In CEPHEUS, more frail patients died, regardless of treatment arm. Causes of death were similar between treatment arms in frail patients, whereas among nonfrail patients, more patients died of progressive disease in the VRd vs DVRd arm. No clear patterns emerged across age subgroups

	Frail		Nonfrail		<70 years		70–<75 years		≥75 years	
MAIA	**DRd (n=168)**	**Rd (n=166)**	**DRd (n=196)**	**Rd (n=199)**	**DRd (n=78)**	**Rd (n=76)**	**DRd (n=129)**	**Rd (n=130)**	**DRd (n=157)**	**Rd (n=159)**
TEAE	22 (13.1)	21 (12.7)	7 (3.6)	10 (5.0)	7 (9.0)	3 (3.9)	6 (4.7)	10 (7.7)	16 (10.2)	18 (11.3)
Progressive disease	30 (17.9)	29 (17.5)	26 (13.3)	40 (20.1)	7 (9.0)	12 (15.8)	22 (17.1)	27 (20.8)	27 (17.2)	30 (18.9)
CEPHEUS	**DVRd (n=48)**	**VRd (n=33)**	**DVRd (n=96)**	**VRd (n=109)**	**DVRd (n=35)**	**VRd (n=35)**	**DVRd (n=68)**	**VRd (n=65)**	**DVRd (n=41)**	**VRd (n=42)**
TEAE	8 (16.7)	6 (18.2)	14 (14.6)	8 (7.3)	5 (14.3)	4 (11.4)	10 (14.7)	5 (7.7)	7 (17.1)	5 (11.9)
Progressive disease	6 (12.5)	4 (12.1)	2 (2.1)	13 (11.9)	2 (5.7)	4 (11.4)	2 (2.9)	9 (13.8)	4 (9.8)	4 (9.5)

AEs, adverse events; DRd, daratumumab + lenalidomide-dexamethasone; DVRd, daratumumab and bortezomib + lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; TEAE, treatment-emergent adverse event; VRd, bortezomib + lenalidomide-dexamethasone.

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MAIA & CEPHEUS: Conclusions

- DRd or DVRd improved PFS, MRD-negativity ≥CR rates, and sustained MRD-negativity rates vs Rd or VRd arms across age and frailty subgroups in both trials
- AEs were consistent with the known profile of each individual drug
- In both trials, within treatment arms, there were trends toward increased incidence of some AEs in older and frail patients compared to younger or non-frail patients

Dara-based regimens improved efficacy outcomes across age and frailty subgroups in the MAIA and CEPHEUS trials, reinforcing Dara-based regimens as SOC in TIE NDMM regardless of age or frailty (based on the simplified frailty index).
These data offer clinically relevant insights to help guide treatment selection for TIE patients

≥CR, complete response or better; AEs, adverse events; Dara, daratumumab; DRd, daratumumab + lenalidomide-dexamethasone; DVRd, daratumumab and bortezomib + lenalidomide-dexamethasone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; Rd, lenalidomide-dexamethasone; SOC, standard of care; TIE, transplant ineligible; VRd, bortezomib + lenalidomide-dexamethasone.

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