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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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Key Takeaway

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

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

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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

Methods

- MAIA and CEPHEUS were randomized, open-label, multicenter, phase 3 trials
- Patients were randomized 1:1 to receive DRd or Rd in MAIA and to receive DVRd or VRd in CEPHEUS
- CEPHEUS enrolled 395 patients with TIE or transplant-deferred NDMM. Only patients with TIE NDMM from CEPHEUS were included in this analysis
- Subgroups included:
  - Age (<70, 70–<75, or ≥75 y)
  - Frailty (assessed using the IFM simplified frailty score at baseline)[6]
    - Nonfrail = score of 0/1
    - Frail = score ≥2
- Efficacy endpoints included progression-free survival (PFS), complete response or better (≥CR) rates, overall minimal residual disease (MRD) negativity (10^{-5} threshold), and sustained MRD negativity

Results

Patient Population

- MAIA[1] included 737 patients (DRd, n=368; Rd, n=369) with a median age of 73 y (range, 45–90)
  - 155 (21%) patients were <70 y, 261 (35%) 70–<75 y, and 321 (44%) ≥75 y; 341 (46%) patients were frail, 88.0% of whom were ≥70 y
- CEPHEUS[3] included 289 TIE patients (DVRd, n=144; VRd, n=145) with a median age of 72 y (range, 51–80); no patients were >80 y
  - 70 (24%) patients were <70 y, 133 (46%) 70–<75 y, and 86 (30%) ≥75 y; 83 (29%) patients were frail, 86% of whom were ≥70 y
- 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 (**Table 1**)
  - Within treatment arms, treatment duration was longer in nonfrail patients, and also generally longer in younger patients

Results (cont)

Table 1: Median (range) duration of study treatment (months) in MAIA and CEPHEUS

	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)

Efficacy

- DRd or DVRd consistently improved overall (**Figure 1A, 2A**) and sustained (**Figure 1B, 2B**) MRD-negativity in both MAIA (**Figure 1**) and CEPHEUS (**Figure 2**)
- Dara improved PFS in MAIA and CEPHEUS TIE patients across most age and frailty subgroups (**Figure 3**)

Figure 1: Overall and sustained MRD-negativity (10^{-5}) ≥CR rates in MAIA

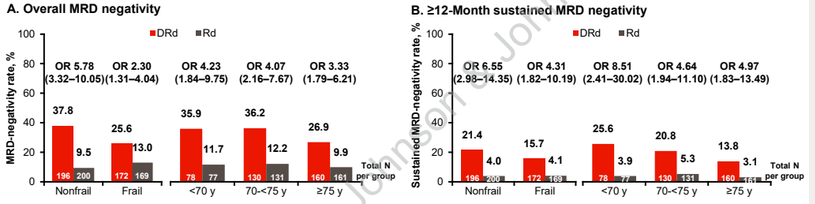


Figure 2: Overall and sustained MRD-negativity (10^{-5}) ≥CR rates in CEPHEUS

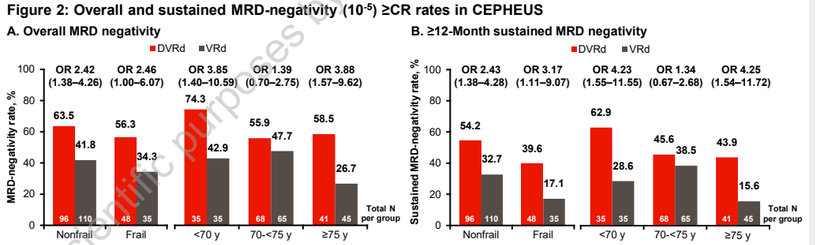
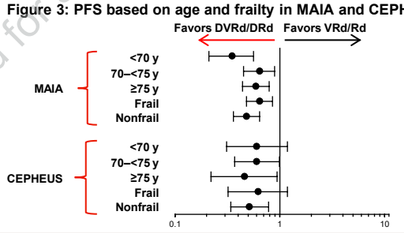


Figure 3: PFS based on age and frailty in MAIA and CEPHEUS



	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)

Safety

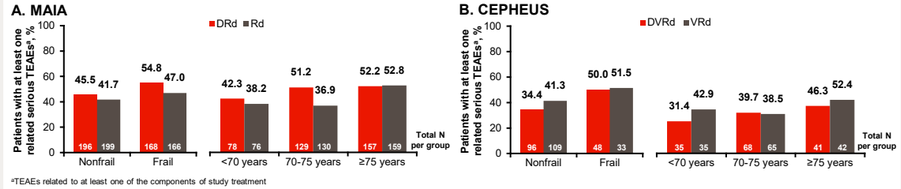
- In MAIA, rates of grade 3/4 TEAEs were generally higher in frail vs nonfrail patients, and in older vs younger patients within treatment arms (**Table 2**). COVID-19 infections/pneumonia were reported in <2% of patients in the DRd arm across subgroups. There were no new safety signals beyond the typical neutropenia and infection TEAEs occurring with DRd
- In CEPHEUS, there were no apparent trends in the incidence of Grade 3/4 TEAEs (**Table 2**), including COVID-19, based on age or frailty. There were no new safety signals beyond the typical hematologic and infection TEAEs occurring with DVRd
- 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 (**Table 2**)
- 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 (**Figure 4A-B**)

Table 2: Most common grade 3/4 TEAEs of interest and treatment-related discontinuations 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.

Figure 4: Related serious TEAEs



[a]TEAEs related to at least one of the components of study treatment

- In MAIA, more patients died in the Rd vs DRd arm, regardless of frailty; 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 (**Table 3**)
- 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 (**Table 3**)

Table 3: Causes of death 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)
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)

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Multiple Myeloma

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