Overall Survival and Progression-free Survival by Treatment Duration With Daratumumab + Lenalidomide/Dexamethasone in Transplant-ineligible Newly Diagnosed Multiple Myeloma: Phase 3 MAIA Study*

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Honoraria: Amgen, Celgene/Bristol Myers Squibb, Janssen, Oncopeptides, and Sanofi

Introduction

- The PFS benefit of daratumumab in combination with standard of care versus standard of care alone in patients with NDMM was established in the phase 3 ALCYONE, MAIA, and CASSIOPEIA studies[1-3]; the OS benefit of a daratumumab-based regimen in patients with NDMM was also established in the ALCYONE study[4]
- VRd was established as a standard-of-care regimen for elderly patients based on results of the phase 3 SWOG S0777 study in patients with NDMM without intent for immediate transplant (69% of whom were intended for eventual transplant)[5]
  - At a median follow-up of 84 months, the median PFS was 41 months for VRd and 29 months for Rd (HR, 0.742); median OS was not reached versus 69 months, respectively (HR, 0.709)[6]
  - 43% of patients in SWOG S0777 were ≥65 years of age (compared with 99% in MAIA); however, a significant OS benefit was not observed in this subgroup for VRd versus Rd (median, 65 months vs 56 months; HR, 0.769; *P* = 0.168)[6]
- Real-world data indicate that >50% of transplant-ineligible elderly patients with NDMM do not receive any subsequent therapy; this suggests that the most effective therapy should be used upfront and not saved for relapse,[7] at which time additional genetic mutations conferring resistance may have been acquired[8]
- In a previous MAIA update (Kumar SK, et al. ASH 2020), D-Rd prolonged PFS and PFS2 versus Rd alone in transplant-ineligible patients with NDMM; OS data were not yet mature[9]

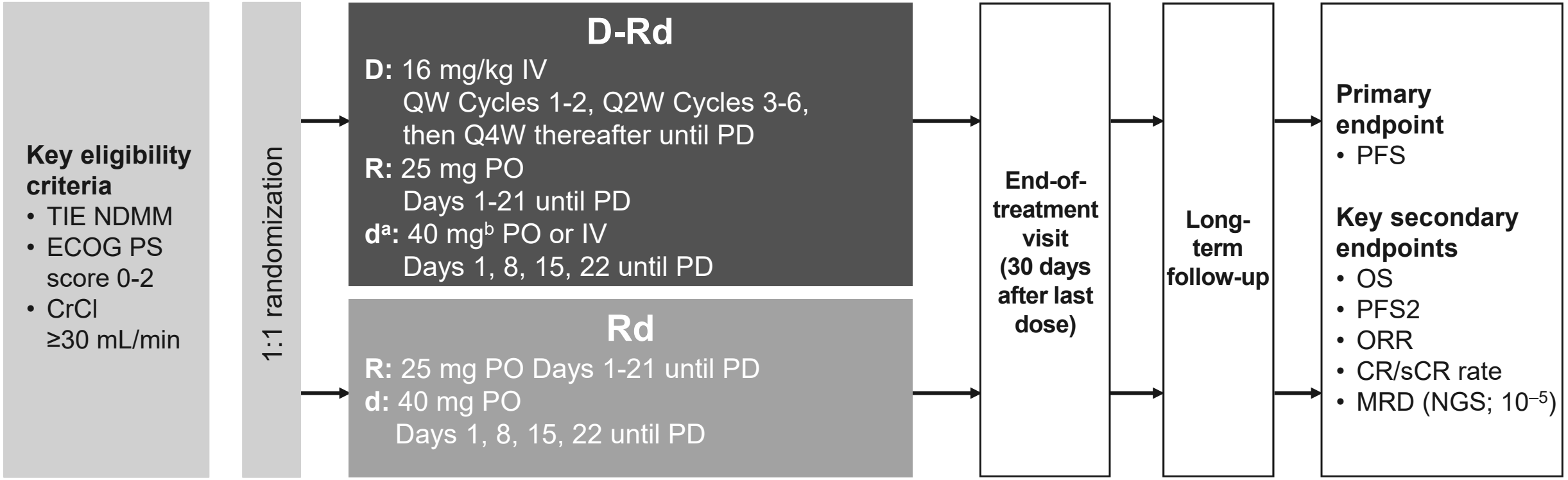
Here, we report updated efficacy and safety results from a pre-specified interim OS analysis of MAIA and a post hoc analysis of PFS by treatment duration after a median follow-up of approximately 56 months

PFS, progression-free survival; NDMM, newly diagnosed multiple myeloma; OS, overall survival; VRd, bortezomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; D-Rd, daratumumab plus lenalidomide/dexamethasone; PFS2, progression-free survival on the next subsequent line of therapy.

1. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528. 2. Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115. 3. Moreau P, et al. *Lancet*. 2019;394(10192):29-38. 4. Mateos MV, et al. *Lancet*. 2020;395(10218):132-141. 5. Durie BGM, et al. *Lancet*. 2017;389(10068):519-527. 6. Durie BGM, et al. *Blood Cancer J*. 2020;10(5):53. 7. Fonseca R, et al. *BMC Cancer*. 2020;20(1):1087. 8. Suzuki K, et al. *Cancers (Basel)*. 2021;13(2):215. 9. Kumar SK, et al. *Blood*. 2020;136(suppl 1):24-26.

MAIA Study Design

- Patients were enrolled in MAIA from March 2015 through January 2017



MAIA is a multicenter, randomized, open-label, active-controlled, phase 3 study of D-Rd versus Rd alone in patients with NDMM who are transplant ineligible

TIE, transplant-ineligible; ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; PD, progressive disease; PO, oral; ORR, overall response rate; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; BMI, body mass index.

[a]On days when daratumumab is administered, dexamethasone will be administered to patients in the D-Rd arm and will serve as the treatment dose of steroid for that day, as well as the required pre-infusion medication. [b]For patients >75 years of age or with BMI <18.5 kg/m^2, dexamethasone was administered at a dose of 20 mg QW.

Demographics and Baseline Characteristics (ITT)

	D-Rd (n = 368)	Rd (n = 369)
Age		
Median (range), y	73 (50-90)	74 (45-89)
Distribution, n (%)		
<65 y	4 (1)	4 (1)
65-<70 y	74 (20)	73 (20)
70-<75 y	130 (35)	131 (36)
≥75 y	160 (43)	161 (44)
Male, n (%)	189 (51)	195 (53)
ECOG PS score,[a] n (%)		
0	127 (35)	123 (33)
1	178 (48)	187 (51)
2[b]	63 (17)	59 (16)
ISS stage,[c] n (%)		
I	98 (27)	103 (28)
II	163 (44)	156 (42)
III	107 (29)	110 (30)

	D-Rd (n = 368)	Rd (n = 369)
Type of measurable disease, n (%)		
IgG	225 (61)	231 (63)
IgA	65 (18)	66 (18)
Other[d]	9 (2)	10 (3)
Detected in urine only	40 (11)	34 (9)
Detected as serum-free light chain only	29 (8)	28 (8)
Cytogenetic profile,[e] n/total n (%)		
Standard risk	271/319 (85)	279/323 (86)
High risk	48/319 (15)	44/323 (14)
Median time since initial diagnosis of MM (range), months	0.95 (0.1-13.3)	0.89 (0-14.5)

Demographics and baseline characteristics were well balanced between arms

ITT, intention-to-treat.

[a]ECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. [b]Two patients had an ECOG PS score >2 (1 patient each with an ECOG PS score of 3 and 4). [c]ISS stage is derived based on the combination of serum β_2-microglobulin and albumin; higher stages indicate more severe disease. [d]Includes IgD, IgE, IgM, and biclonal. [e]Cytogenetic abnormalities were identified by fluorescence in situ hybridization or karyotype testing; high risk was defined as having a t(4;14), t(14;16), and/or del17p abnormality.

Note: percentages may not add up to 100% due to rounding.

Treatment Exposure and Patient Disposition

Median duration of follow-up: 56.2 months

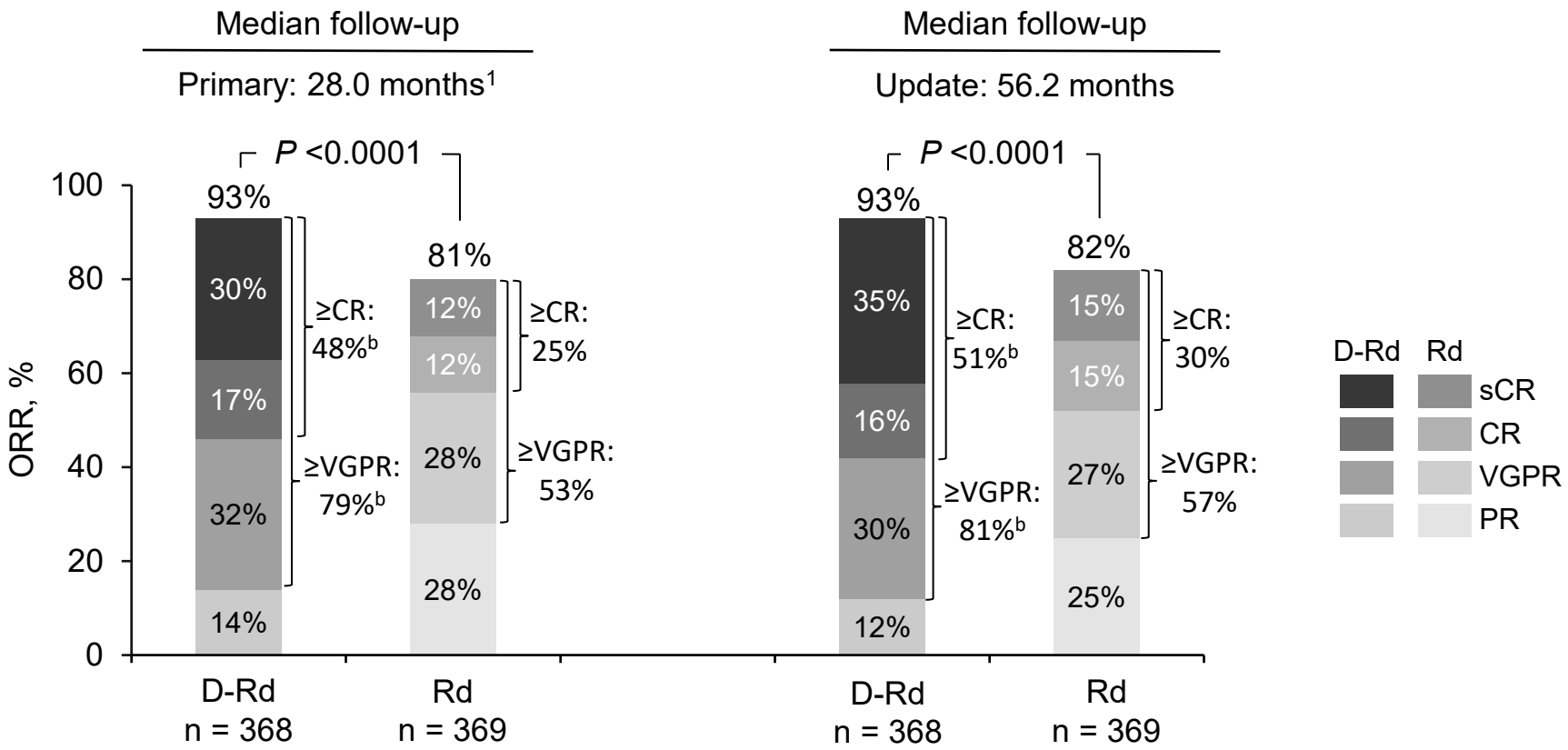
Safety population (received ≥1 dose of study treatment)	D-Rd (n = 364)	Rd (n = 365)
Median duration of study treatment, months (range)	47.5 (0.10-69.26)	22.6 (0.03-69.22)
Lenalidomide median RDI, % (range)	66 (8-206)	86 (5-239)
Discontinued lenalidomide only while continuing other study treatment, n (%)	33 (9)	14 (4)
IV daratumumab median RDI, % (range)	98 (3-107)	–
Discontinued daratumumab only while continuing other study treatment, n (%)	5 (1)	–

ITT population	D-Rd (n = 368)	Rd (n = 369)
Remaining on study treatment, %	42	18
Discontinued study treatment, %	57	81
Progressive disease	27	34
Adverse event	13	23
Death	7	7
Noncompliance with study drug	5	8
Physician decision	4	6
Other	1	1
Lost to follow-up	<1	1
Patient withdrawal	0	2

42% of patients in the D-Rd arm and 18% of patients in the Rd arm remained on treatment; more patients in the Rd arm than in the D-Rd arm discontinued due to AEs

RDI, relative dose intensity; AE, adverse event.
Note: percentages may not add up to 100% due to rounding.

ORR[a]



- **D-Rd induced deeper responses, with significantly higher rates of ≥CR and ≥VGPR, compared with Rd**
- **With >28 months of additional follow-up, responses deepened with continued daratumumab therapy**

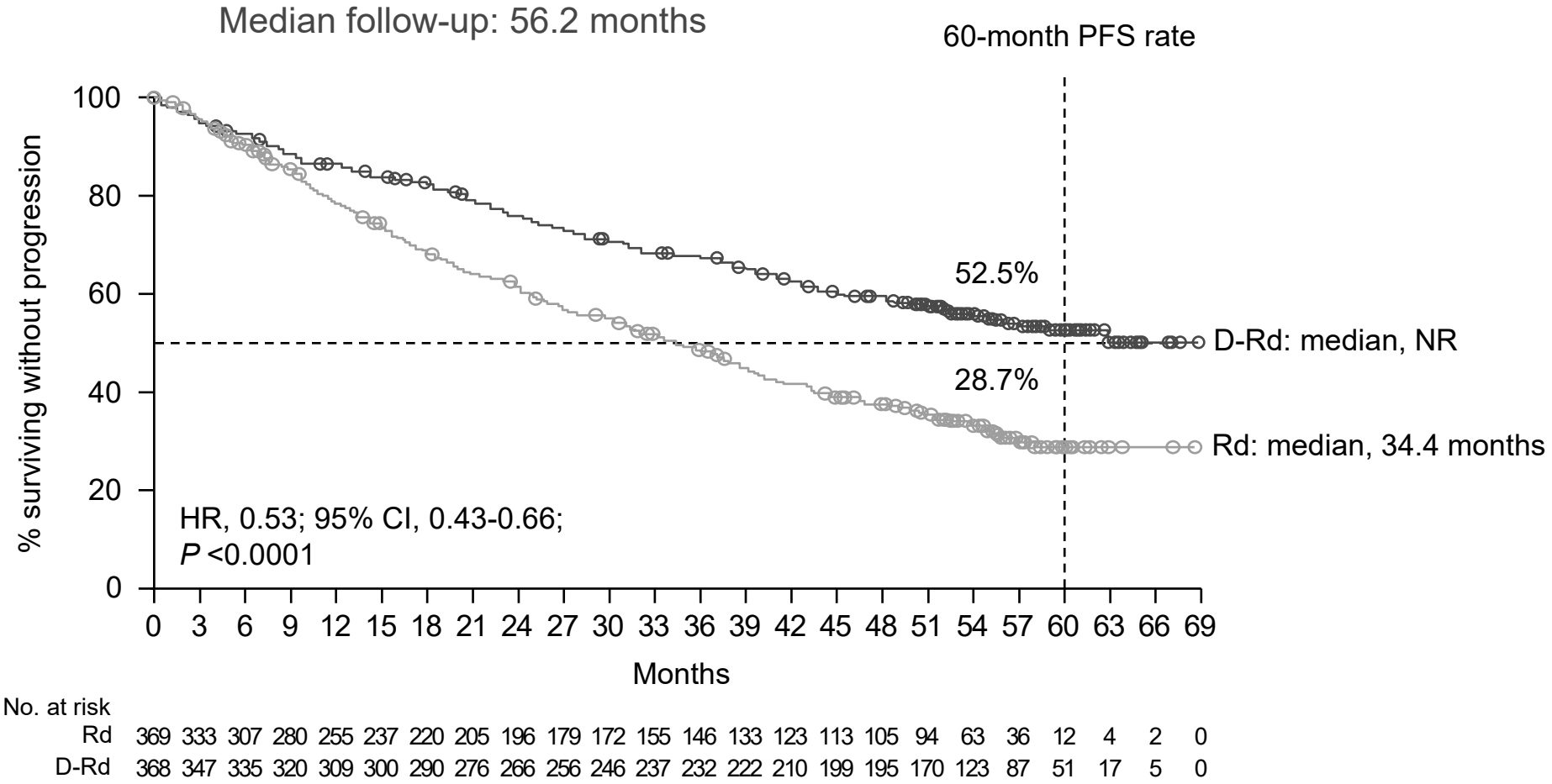
VGPR, very good partial response; PR, partial response; OR, odds ratio.

[a]ITT population. [b]*P* <0.0001; *P* values were calculated from the Cochran–Mantel–Haenszel chi-squared test.

1. Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115.

Note: percentages may not add up to the total due to rounding.

Updated PFS

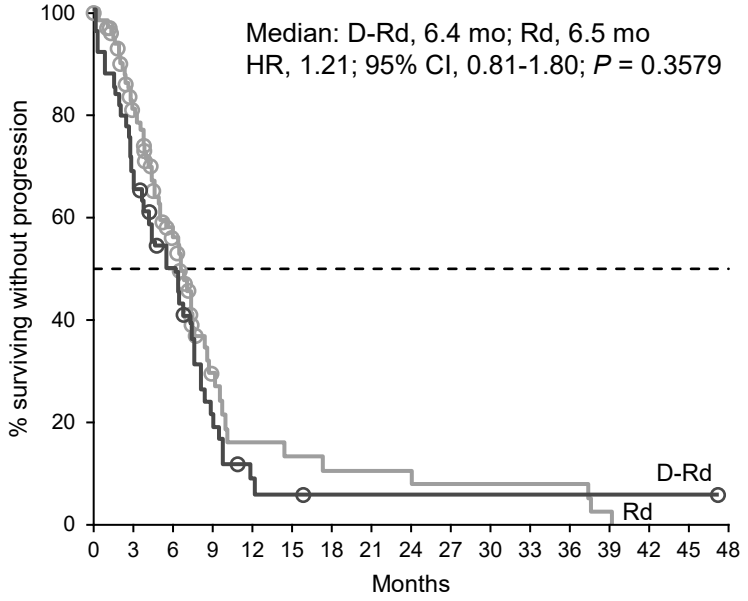


- **D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd**
- **These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible**

NR, not reached; CI, confidence interval.

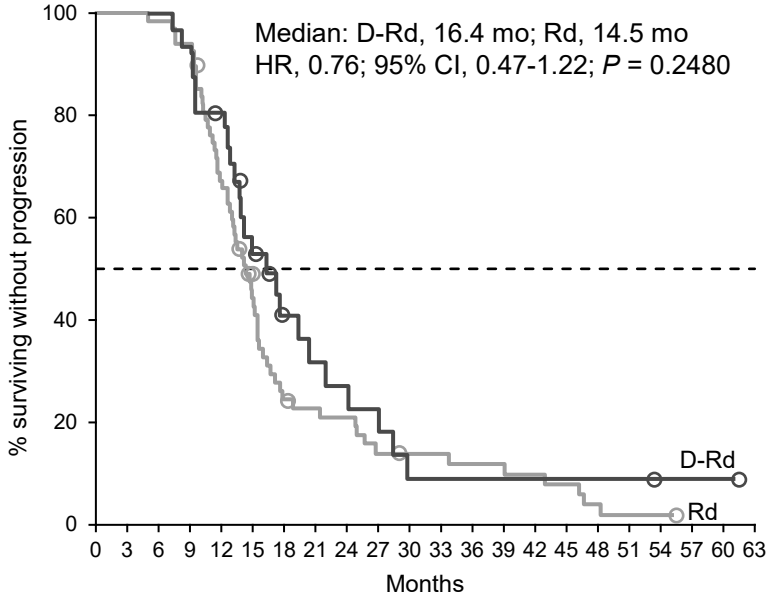
PFS by Duration of Treatment[a]

Patients who received <9 months of treatment



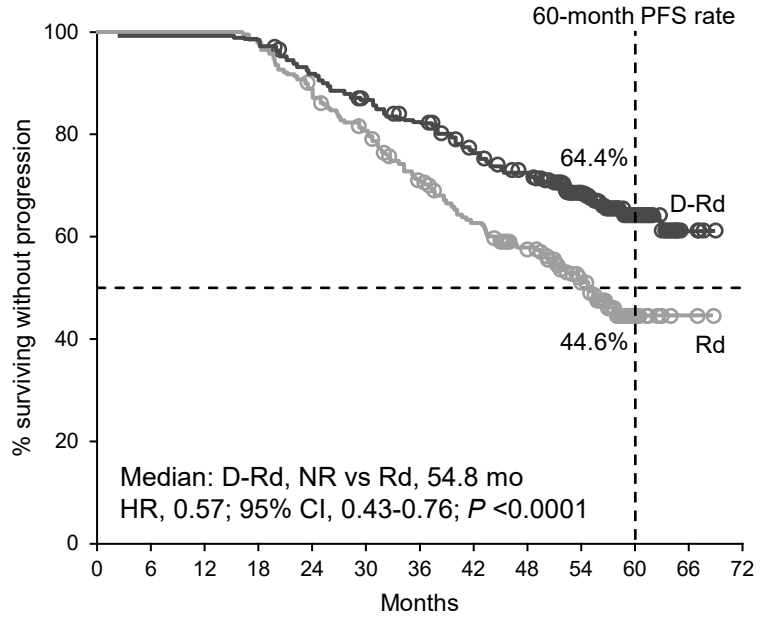
No. at risk																	
Rd	93	61	36	12	6	5	4	4	4	3	3	3	3	1	0	0	0
D-Rd	50	34	22	9	3	2	1	1	1	1	1	1	1	1	1	1	0

Patients who received ≥9-<18 months of treatment



No. at risk																								
Rd	68	68	67	64	45	28	15	13	12	8	7	7	6	6	5	4	2	1	1	0	0	0		
D-Rd	31	31	31	29	24	16	9	7	6	5	2	2	2	2	2	2	2	2	1	1	1	0		

Patients who received ≥18 months of treatment

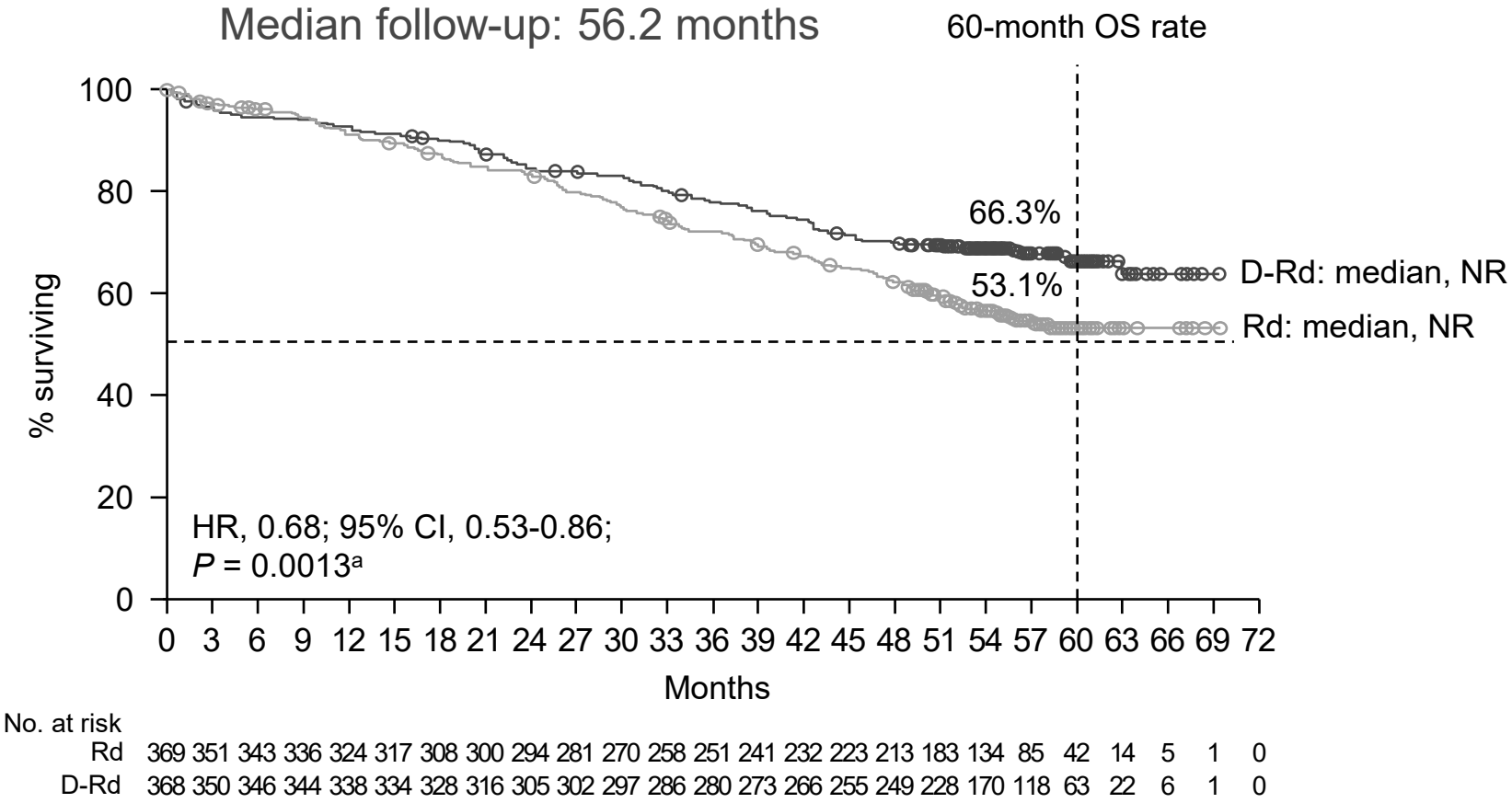


No. at risk																								
Rd	204	204	204	201	180	162	137	118	103	62	12	2	0											
D-Rd	283	282	282	280	259	243	229	207	193	122	50	5	0											

D-Rd showed a robust PFS benefit among patients treated for ≥18 months, with a 43% reduction in the risk of disease progression or death and a 20% increase in PFS rate at 60 months

[a]Post hoc analysis.

OS

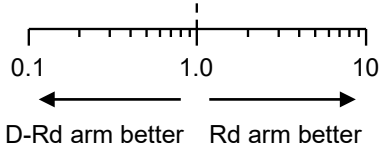


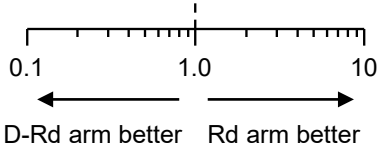
D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

[a]*P* = 0.0013 is statistically significant, crossing the pre-specified stopping boundary of *P* = 0.0414.

Subgroup Analysis of OS

	D-Rd No. of deaths/ total no.	Rd No. of deaths/ total no.	D-Rd Median OS (months)	Rd Median OS (months)	HR (95% CI)
Sex					
Male	71/189	88/195	NE	57.2	0.78 (0.57-1.06)
Female	46/179	68/174	NE	NE	0.58 (0.40-0.84)
Age					
<75 years	52/208	80/208	NE	NE	0.60 (0.42-0.85)
≥75 years	65/160	76/161	NE	55.7	0.76 (0.55-1.06)
Race					
White	106/336	138/339	NE	NE	0.71 (0.55-0.91)
Other	11/32	18/30	NE	49.1	0.48 (0.23-1.03)
Region					
North America	33/101	46/102	NE	55.7	0.63 (0.40-0.98)
Other	84/267	110/267	NE	NE	0.70 (0.53-0.93)
Baseline renal function (CrCl)					
>60 mL/min	59/206	89/227	NE	NE	0.66 (0.48-0.92)
≤60 mL/min	58/162	67/142	NE	54.8	0.67 (0.47-0.96)
Baseline hepatic function					
Normal	104/335	144/340	NE	NE	0.65 (0.51-0.84)
Impaired	13/31	12/29	NE	NE	1.05 (0.48-2.30)
ISS disease stage					
I	19/98	24/103	NE	NE	0.79 (0.43-1.44)
II	50/163	69/156	NE	NE	0.61 (0.42-0.88)
III	48/107	63/110	62.8	47.3	0.72 (0.49-1.04)
Type of MM					
IgG	74/225	90/231	NE	NE	0.80 (0.59-1.09)
Non-IgG	22/74	37/76	NE	53.7	0.50 (0.30-0.86)
Cytogenetic risk at study entry					
High risk	25/48	26/44	55.6	42.5	0.80 (0.46-1.39)
Standard risk	80/271	116/279	NE	NE	0.64 (0.48-0.85)
ECOG PS score					
0	24/127	36/123	NE	NE	0.61 (0.36-1.02)
1	64/178	82/187	NE	58.3	0.74 (0.53-1.03)
≥2	29/63	38/59	62.8	39.0	0.57 (0.35-0.94)





OS benefit with D-Rd was generally consistent across patient subgroups

NE, not estimable.

Subsequent Therapy

- Median time to next treatment was not reached with D-Rd versus 42.4 months with Rd (HR, 0.47; 95% CI, 0.37-0.59; *P* <0.0001)
- 114 patients in the D-Rd arm and 186 patients in the Rd arm received subsequent therapy; of these:
  - A PI-containing regimen without an IMiD was the most common first subsequent therapy (53% vs 54% with D-Rd and Rd, respectively)
  - 15% of patients in the D-Rd arm and 46% of patients in the Rd arm received a daratumumab-containing regimen as any subsequent line of therapy

PI, proteasome inhibitor; IMiD, immunomodulatory drug.

Most Common (>5%) Grade 3/4 TEAEs (Safety Population)[a]

	D-Rd (n = 364)	Rd (n = 365)
Hematologic, n (%)		
Neutropenia	197 (54)	135 (37)
Anemia	61 (17)	79 (22)
Lymphopenia	60 (16)	41 (11)
Leukopenia	42 (12)	23 (6)
Thrombocytopenia	32 (9)	34 (9)
Nonhematologic, n (%)		
Pneumonia	70 (19)	39 (11)
Hypokalemia	46 (13)	36 (10)
Cataract	40 (11)	39 (11)
Diarrhea	32 (9)	22 (6)
Fatigue	32 (9)	17 (5)
Hypertension	31 (9)	16 (4)
Hyperglycemia	28 (8)	14 (4)
Pulmonary embolism	26 (7)	19 (5)
Asthenia	19 (5)	17 (5)
Acute kidney injury	19 (5)	12 (3)
Chronic kidney disease	19 (5)	10 (3)

No new safety concerns were identified with longer follow-up

TEAE, treatment-emergent adverse event.

[a]Median duration of study treatment was 47.5 months in the D-Rd arm and 22.6 months in the Rd arm. Data are not exposure adjusted.

Conclusions

- After almost 5 years of follow-up, a significant OS benefit of D-Rd versus Rd given to progression was demonstrated in patients with transplant-ineligible NDMM, representing a 32% reduction in the risk of death
  - The estimated 5-year OS rate was 66.3% with D-Rd and 53.1% with Rd, which will likely lead to a substantial improvement of median OS in this patient population
- The significant PFS benefit of D-Rd versus Rd was maintained, with a 47% reduction in the risk of disease progression or death (median PFS for D-Rd, not reached)
  - The estimated 5-year PFS rate was 52.5% with D-Rd and 28.7% with Rd
  - These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible
  - In a post hoc analysis, D-Rd showed a robust PFS benefit versus Rd among patients treated for ≥18 months
- These PFS and OS results have been achieved in a study population with 44% of patients aged 75 to 90 years
- No new safety concerns were identified with continuous therapy and longer follow-up

These results strongly support upfront D-Rd as a new standard of care for patients with transplant-ineligible NDMM

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- All investigators who contributed to the study
  - Intergroupe Francophone du Myélome
- Staff members at the study sites
- Data and safety monitoring committee
- Staff members involved in data collection and analyses

MAIA

14 countries

- Other ongoing frontline registration daratumumab studies include:
  - Transplant ineligible: CEPHEUS (D-VRd)
  - Transplant eligible: PERSEUS (D-VRd)

D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone.

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