Supplemental Material

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: San-Miguel J, Avet-Loiseau H, Paiva B, et al. Sustained Minimal Residual Disease Negativity in Newly Diagnosed Multiple Myeloma and the Impact of Daratumumab in MAIA and ALCYONE

Supplemental Table 1. Summary of Diagnostic or Baseline Bone Marrow Aspirate Sample Calibration Rate Based on the ClonoSEQ V2.0 Assay Among Patients in the ITT Population who Achieved a Best Response of ≥CR

	MAIA			ALCYONE		
	D-Rd	**Rd**	**Total**	**D-VMP**	**VMP**	**Total**
Analysis set: ITT with ≥CR	n = 182	n = 100	n = 282	n = 160	n = 90	n = 250
Patients with sample for testing[a]	179 (98.4%)	95 (95.0%)	274 (97.2%)	153 (95.6%)	83 (92.2%)	236 (94.4%)
Patients with calibration success[b,c]	168 (93.9%)	87 (91.6%)	255 (93.1%)	142 (92.8%)	75 (90.4%)	217 (91.9%)
Patients with calibration failure[b,d]	7 (3.9%)	6 (6.3%)	13 (4.7%)	8 (5.2%)	8 (9.6%)	16 (6.8%)
Patients with unsuccessful assay run[b,e]	4 (2.2%)	2 (2.1%)	6 (2.2%)	3 (2.0%)	0	3 (1.3%)
Patients without sample for testing[a,f]	3 (1.6%)	5 (5.0%)	8 (2.8%)	7 (4.4%)	7 (7.8%)	14 (5.6%)

ITT, intent-to-treat; CR, complete response; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

[a]Percentages calculated with the number of patients in each treatment group as the denominator.

[b]Percentages calculated with the number of patients with sample for testing as the denominator.

[c]Patients with multiple baseline samples, of which at least one successfully calibrated, are counted as calibration success only.

[d]Sample with no clone identified.

[e]Sample failed QC or not enough DNA.

[f]Includes patients that do not have either or both of a diagnostic or baseline and on-treatment sample collected and available.

Supplemental Table 2. Demographic and Baseline Disease Characteristics in Patients in MAIA Based on MRD Durability

Characteristic	MAIA											
	D-Rd						Rd					
		MRD-negative patients						MRD-negative patients				
	ITT (n = 368)	At any time (n = 106)	≥6 months (n = 55)	Not ≥6 months (n = 51)	≥12 months (n = 40)	Not ≥12 months (n = 66)	ITT (n = 369)	At any time (n = 34)	≥6 months (n = 16)	Not ≥6 months (n = 18)	≥12 months (n = 9)	Not ≥12 months (n = 25)
Age												
Median (range), years	73.0 (50-90)	72.0 (65-87)	72.0 (66-85)	73.0 (65-87)	71.0 (66-85)	73.5 (65-87)	74.0 (45-89)	72.5 (66-87)	72.5 (66-87)	72.5 (68-84)	71.0 (69-78)	73.0 (66-87)
Distribution, n (%)												
<75 years	208 (56.5%)	68 (64.2%)	37 (67.3%)	31 (60.8%)	31 (77.5%)	37 (56.1%)	208 (56.4%)	20 (58.8%)	9 (56.3%)	11 (61.1%)	6 (66.7%)	14 (56.0%)
≥75 years	160 (43.5%)	38 (35.8%)	18 (32.7%)	20 (39.2%)	9 (22.5%)	29 (43.9%)	161 (43.6%)	14 (41.2%)	7 (43.8%)	7 (38.9%)	3 (33.3%)	11 (44.0%)
Sex, n (%)												
Male	189 (51.4%)	58 (54.7%)	34 (31.8%)	24 (47.1%)	25 (62.5%)	33 (50.0%)	195 (52.8%)	23 (67.6%)	8 (50.0%)	15 (83.3%)	5 (55.6%)	18 (72.0%)
Female	179 (48.6%)	48 (45.3%)	21 (38.2%)	27 (52.9%)	15 (37.5%)	33 (50.0%)	174 (47.2%)	11 (32.4%)	8 (50.0%)	3 (16.7%)	4 (44.4%)	7 (28.0%)
Race, n (%)												
White	336 (91.3%)	101 (95.3%)	54 (98.2%)	47 (92.2%)	39 (97.5%)	62 (93.9%)	339 (91.9%)	33 (97.1%)	16 (100.0%)	17 (94.4%)	9 (100.0%)	24 (96.0%)
Non-White[a]	32 (8.7%)	5 (4.7%)	1 (1.8%)	4 (7.8%)	1 (2.5%)	4 (6.1%)	30 (8.1%)	1 (2.9%)	0	1 (5.6%)	0	1 (4.0%)
ECOG performance status, n (%)												
0	127 (34.5%)	42 (39.6%)	20 (36.4%)	22 (43.1%)	12 (30.0%)	30 (45.5%)	123 (33.3%)	8 (23.5%)	2 (12.5%)	6 (33.3%)	2 (22.2%)	6 (24.0%)
1	178 (48.4%)	47 (44.3%)	24 (43.6%)	23 (45.1%)	18 (45.0%)	29 (43.9%)	187 (50.7%)	15 (44.1%)	10 (62.5%)	5 (27.8%)	6 (66.7%)	9 (36.0%)
≥2	63 (17.1%)	17 (16.0%)	11 (20.0%)	6 (11.8%)	10 (25.0%)	7 (10.6%)	59 (16.0%)	11 (32.4%)	4 (25.0%)	7 (38.9%)	1 (11.1%)	10 (40.0%)
Type of measurable disease, n (%)												
IgG	225 (61.1%)	57 (53.8%)	17 (30.9%)	22 (43.1%)	12 (30.0%)	27 (40.9%)	231 (62.6%)	24 (70.6%)	10 (62.5%)	11 (61.1%)	7 (77.8%)	14 (56.0%)
IgA	65 (17.7%)	27 (25.5%)	11 (20.0%)	9 (17.6%)	7 (17.5%)	13 (19.7%)	66 (17.9%)	5 (14.7%)	3 (18.8%)	2 (11.1%)	0	5 (20.0%)
Detected in urine only	40 (10.9%)	15 (14.2%)	8 (14.5%)	7 (13.7%)	7 (17.5%)	8 (12.1%)	34 (9.2%)	1 (2.9%)	1 (6.3%)	0	0	1 (4.0%)
Detected in serum free light chains only	29 (7.9%)	7 (6.6%)	2 (3.6%)	5 (9.8%)	0	7 (10.6%)	28 (7.6%)	3 (8.8%)	1 (6.3%)	2 (11.1%)	1 (11.1%)	2 (8.0%)
ISS disease stage[b], n (%)												
I	98 (26.6%)	24 (22.6%)	11 (20.0%)	13 (25.5%)	10 (25.0%)	14 (21.2%)	103 (27.9%)	11 (32.4%)	6 (37.5%)	5 (27.8%)	5 (55.6%)	6 (24.0%)
II	163 (44.3%)	55 (51.9%)	30 (54.5%)	25 (49.0%)	19 (47.5%)	36 (54.5%)	156 (42.3%)	15 (44.1%)	6 (37.5%)	9 (50.0%)	3 (33.3%)	12 (48.0%)
III	107 (29.1%)	27 (25.5%)	14 (25.5%)	13 (25.5%)	11 (27.5%)	16 (24.2%)	110 (29.8%)	8 (23.5%)	4 (25.0%)	4 (22.2%)	1 (11.1%)	7 (28.0%)
Cytogenetic profile[c]												

Patients evaluated	319	96	47	49	34	62	323	27	12	15	8	19
Standard-risk cytogenetic abnormality, n (%)	271 (85.0%)	85 (88.5%)	42 (89.4%)	43 (87.8%)	29 (85.3%)	56 (90.3%)	279 (86.4%)	26 (96.3%)	12 (100.0%)	14 (93.3%)	8 (100.0%)	18 (94.7%)
High-risk cytogenetic abnormality[d], n (%)	48 (15.0%)	11 (11.5%)	5 (10.6%)	6 (12.2%)	5 (14.7%)	6 (9.7%)	44 (13.6%)	1 (3.7%)	0	1 (6.7%)	0	1 (5.3%)
del(17p)	25 (7.8%)	6 (6.3%)	2 (4.3%)	4 (8.2%)	2 (5.9%)	4 (6.5%)	29 (9.0%)	0	0	0	0	0
Median time since initial diagnosis of multiple myeloma (months)	0.95	0.94	0.85	1.15	0.69	1.18	0.89	0.89	1.07	0.76	1.08	0.76

MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ITT, intent to treat; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; ISS, International Staging System.

All data are n (%), unless otherwise indicated.

[a]Includes Black or African-American, Asian, other, unknown, and not reported.

[b]ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

[c]Cytogenetic risk status was determined by fluorescence in situ hybridization or karyotype testing.

[d]High risk is defined as having a positive test for any of the del17p, t(14;16), or t(4;14) molecular abnormalities.

Supplemental Table 3. Demographic and Baseline Disease Characteristics in Patients in ALCYONE Based on MRD Durability

Characteristic	ALCYONE											
	D-VMP						VMP					
		MRD-negative patients						MRD-negative patients				
	ITT (n = 350)	At any time (n = 94)	≥6 months (n = 55)	Not ≥6 months (n = 39)	≥12 months (n = 49)	Not ≥12 months (n = 45)	ITT (n = 356)	At any time (n = 25)	≥6 months (n = 16)	Not ≥6 months (n = 9)	≥12 months (n = 10)	Not ≥12 months (n = 15)
Age												
Median (range), years	71.0 (40-93)	71.0 (40-93)	71.0 (40-87)	71.0 (56-93)	71.0 (40-87)	71.0 (56-93)	71.0 (50-91)	73.0 (52-82)	73.0 (52-82)	74.0(67-81)	72.0 (52-82)	74.0 (67-82)
Distribution, n (%)												
<75 years	246 (70.3%)	68 (72.3%)	39 (70.9%)	29 (74.4%)	36 (73.5%)	32 (71.1%)	249 (69.9%)	15 (60.0%)	10 (62.5%)	5 (55.6%)	6 (60.0%)	9 (60.0%)
≥75 years	104 (29.7%)	26 (27.7%)	16 (29.1%)	10 (25.6%)	13 (26.5%)	13 (28.9%)	107 (30.1%)	10 (40.0%)	6 (37.5%)	4 (44.4%)	4 (40.0%)	6 (40.0%)
Sex, n (%)												
Male	160 (45.7%)	35 (37.2%)	17 (30.9%)	18 (46.2%)	14 (28.6%)	21 (46.7%)	167 (46.9%)	10 (40.0%)	5 (31.3%)	5 (55.6%)	4 (40.0%)	6 (40.0%)
Female	190 (54.3%)	59 (62.8%)	38 (69.1%)	21 (53.8%)	35 (71.4%)	24 (53.3%)	189 (53.1%)	15 (60.0%)	11 (68.8%)	4 (44.4%)	6 (60.0%)	9 (60.0%)
Race, n (%)												
White	297 (84.9%)	76 (80.9%)	47 (85.5%)	29 (74.4%)	41 (83.7%)	35 (77.8%)	304 (85.4%)	23 (92.0%)	14 (87.5%)	9 (100.0%)	8 (80.0%)	15 (100.0%)
Non-White[a]	53 (15.1%)	18 (19.1%)	8 (14.5%)	10 (25.6%)	8 (16.3%)	10 (22.2%)	52 (14.6%)	2 (8.0%)	2 (12.5%)	0	2 (20.0%)	0
ECOG performance status, n (%)												
0	78 (22.3%)	17 (18.1%)	11 (20.0%)	6 (15.4%)	11 (22.4%)	6 (13.3%)	99 (27.8%)	7 (28.0%)	4 (25.0%)	3 (33.3%)	2 (20.0%)	5 (33.3%)
1	182 (52.0%)	51 (54.3%)	27 (49.1%)	24 (61.5%)	22 (44.9%)	29 (64.4%)	173 (48.6%)	10 (40.0%)	8 (50.0%)	2 (22.2%)	4 (40.0%)	6 (40.0%)
2	90 (25.7%)	26 (27.7%)	17 (30.9%)	9 (23.1%)	16 (32.7%)	10 (22.2%)	84 (23.6%)	8 (32.0%)	4 (25.0%)	4 (44.4%)	4 (40.0%)	4 (26.7%)
Type of measurable disease, n (%)												
IgG	143 (40.9%)	31 (33.0%)	19 (34.5%)	12 (30.8%)	18 (36.7%)	13 (28.9%)	140 (39.3%)	8 (32.0%)	4 (25.0%)	4 (44.4%)	4 (40.0%)	4 (26.7%)
IgA	49 (14.0%)	12 (12.8%)	7 (12.7%)	5 (12.8%)	6 (12.2%)	6 (13.3%)	53 (14.9%)	5 (20.0%)	4 (25.0%)	1 (11.1%)	1 (10.0%)	4 (26.7%)
Detected in urine only	43 (12.3%)	16 (17.0%)	12 (21.8%)	4 (10.3%)	11 (22.4%)	5 (11.1%)	37 (10.4%)	7 (28.0%)	5 (31.3%)	2 (22.2%)	3 (30.0%)	4 (26.7%)
Detected in serum free light chains only	18 (5.1%)	7 (7.4%)	3 (5.5%)	4 (10.3%)	2 (4.1%)	5 (11.1%)	18 (5.1%)	2 (8.0%)	1 (6.3%)	1 (11.1%)	1 (10.0%)	1 (6.7%)

ISS disease stage[b], n (%)												
I	69 (19.7%)	16 (17.0%)	9 (16.4%)	7 (17.9%)	9 (18.4%)	7 (15.6%)	67 (18.8%)	5 (20.0%)	3 (18.8%)	2 (22.2%)	2 (20.0%)	3 (20.0%)
II	139 (39.7%)	39 (41.5%)	25 (45.5%)	14 (35.9%)	23 (46.9%)	16 (35.6%)	160 (44.9%)	10 (40.0%)	6 (37.5%)	4 (44.4%)	5 (50.0%)	5 (33.3%)
III	142 (40.6%)	39 (41.5%)	21 (38.2%)	18 (46.2%)	17 (34.7%)	22 (48.9%)	129 (36.2%)	10 (40.0%)	7 (43.8%)	3 (33.3%)	3 (30.0%)	7 (46.7%)
Cytogenetic profile[c]												
Patients evaluated	314	88	52	36	46	42	302	23	14	9	9	14
Standard-risk cytogenetic abnormality, n (%)	261 (83.1%)	74 (84.1%)	46 (88.5%)	28 (77.8%)	40 (87.0%)	34 (81.0%)	257 (85.1%)	19 (82.6%)	11 (78.6%)	8 (88.9%)	7 (77.8%)	12 (85.7%)
High-risk cytogenetic abnormality[d], n (%)	53 (16.9%)	14 (15.9%)	6 (11.5%)	8 (22.2%)	6 (13.0%)	8 (19.0%)	45 (14.9%)	4 (17.4%)	3 (21.4%)	1 (11.1%)	2 (22.2%)	2 (14.3%)
del(17p)	29 (9.2%)	8 (9.1%)	4 (7.7%)	4 (11.1%)	4 (8.7%)	4 (9.5%)	27 (8.9%)	3 (13.0%)	2 (14.3%)	1 (11.1%)	1 (11.1%)	2 (14.3%)
Median time since initial diagnosis of multiple myeloma (months)	0.76	0.79	0.92	0.66	0.92	0.66	0.82	0.85	1.05	0.69	1.40	0.69

MRD, minimal residual disease; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ITT, intent to treat; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; ISS, International Staging System.

All data are n (%), unless otherwise indicated.

[a]Includes Black or African-American, Asian, other, unknown, and not reported.

[b]ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

[c]Cytogenetic risk status was determined by fluorescence in situ hybridization or karyotype testing.

[d]High risk is defined as having a positive test for any of the del17p, t(14;16) or t(4;14) molecular abnormalities.

Supplemental Table 4. Progression-free Survival on Next Subsequent Line of Therapy Based on MRD Status

	MAIA		ALCYONE	
	D-Rd	**Rd**	**D-VMP**	**VMP**
	n = 368 (ITT)	**n = 369 (ITT)**	**n = 350 (ITT)**	**n = 356 (ITT)**
PFS2[a]				
MRD negative (10^{-5}) at ≥1 time point, n (%)[b]	106 (28.8%)	34 (9.2%)	94 (26.9%)	25 (7.0%)
Number of events (%); number censored (%)[c]	6 (5.7%); 100 (94.3%)	4 (11.8%); 30 (88.2%)	15 (16.0%); 79 (84.0%)	4 (16.0%); 21 (84.0%)
Median (95% CI), months	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)	NR (40.7-NE)
HR (95% CI), *P* value	0.43 (0.12-1.55); *P* = 0.1853[d]		1.02 (0.34-3.09); *P* = 0.9668[d]	
36-month PFS2 rate, % (95% CI)	95.0 (88.4-97.9)	83.9 (61.3-93.9)	87.0 (78.2-92.4)	92.0 (71.6-97.9)
MRD positive, n (%)[b]	262 (71.2%)	335 (90.8%)	256 (73.1%)	331 (93.0%)
Number of events (%); number censored (%)[c]	90 (34.4%); 172 (65.6%)	117 (34.9%); 218 (65.1%)	87 (34.0%); 169 (66.0%)	148 (44.7%); 183 (55.3%)
Median (95% CI), months	NR (41.0-NE)	47.3 (39.2-NE)	NR (NE-NE)	38.0 (34.1-NE)
HR (95% CI), *P* value	0.90 (0.68-1.18); *P* = 0.4457[e]		0.64 (0.49-0.83); *P* = 0.0008[d]	
36-month PFS2 rate, % (95% CI)	65.5 (59.0-71.3)	61.5 (55.3-67.0)	67.9 (61.6-73.5)	51.9 (45.9-57.6)

MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ITT, intent-to-treat; CI, confidence interval; NR, not reached; NE, not evaluable; HR, hazard ratio; PFS2, progression-free survival on next subsequent line of therapy.

[a]PFS2 was defined as the time from randomization to progression on the next line of treatment or death, whichever came first. Disease progression was based on investigator judgment. For those patients who were still alive and not yet progressed on the next line of treatment, they were censored on the last date of follow-up.
[b]Percentages calculated using the total number of patients in each column heading (ITT population) as the denominator.
[c]Percentages calculated using the number of patients in each column from the row immediately above the number of events (%); number censored (%).
[d]HR and 95% CI from a Cox proportional hazards model with treatment group as the sole explanatory variable. A hazard ratio <1 indicates an advantage for D-Rd or D-VMP. *P* value is based on the log-rank test.

Supplemental Table 5. Cox Proportional Hazards Model for PFS with Time-varying Covariates for MRD Status.

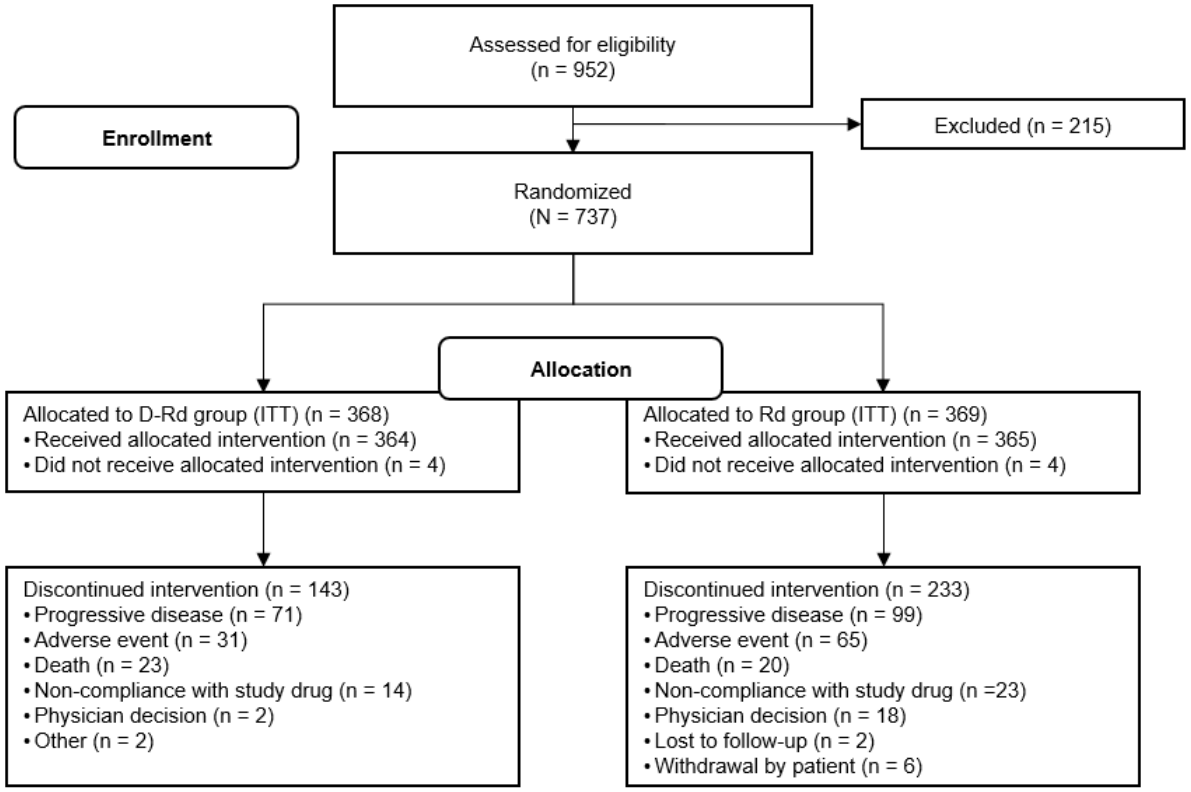
Variable	Hazard ratio (95% CI)	*P* value
Univariate analysis		
Response group (MRD negative vs MRD positive)	0.18 (0.11-0.28)	<0.0001
Multivariate analysis		
Response group (MRD negative vs MRD positive)	0.18 (0.11-0.29)	<0.0001
Age	1.00 (0.98-1.01)	0.533
ISS disease stage (II vs I)	1.77 (1.41-2.22)	<0.0001
ISS disease stage (III vs I)	1.97 (1.54-2.51)	<0.0001
Baseline renal function (>60 mL/min vs ≤60 mL/min)	1.02 (0.86-1.22)	0.786
Cytogenetic risk (high vs standard)	1.52 (1.25-1.86)	<0.0001

PFS, progression-free survival; MRD, minimal residual disease; CI, confidence interval; ISS, International Staging System; CR, complete response.

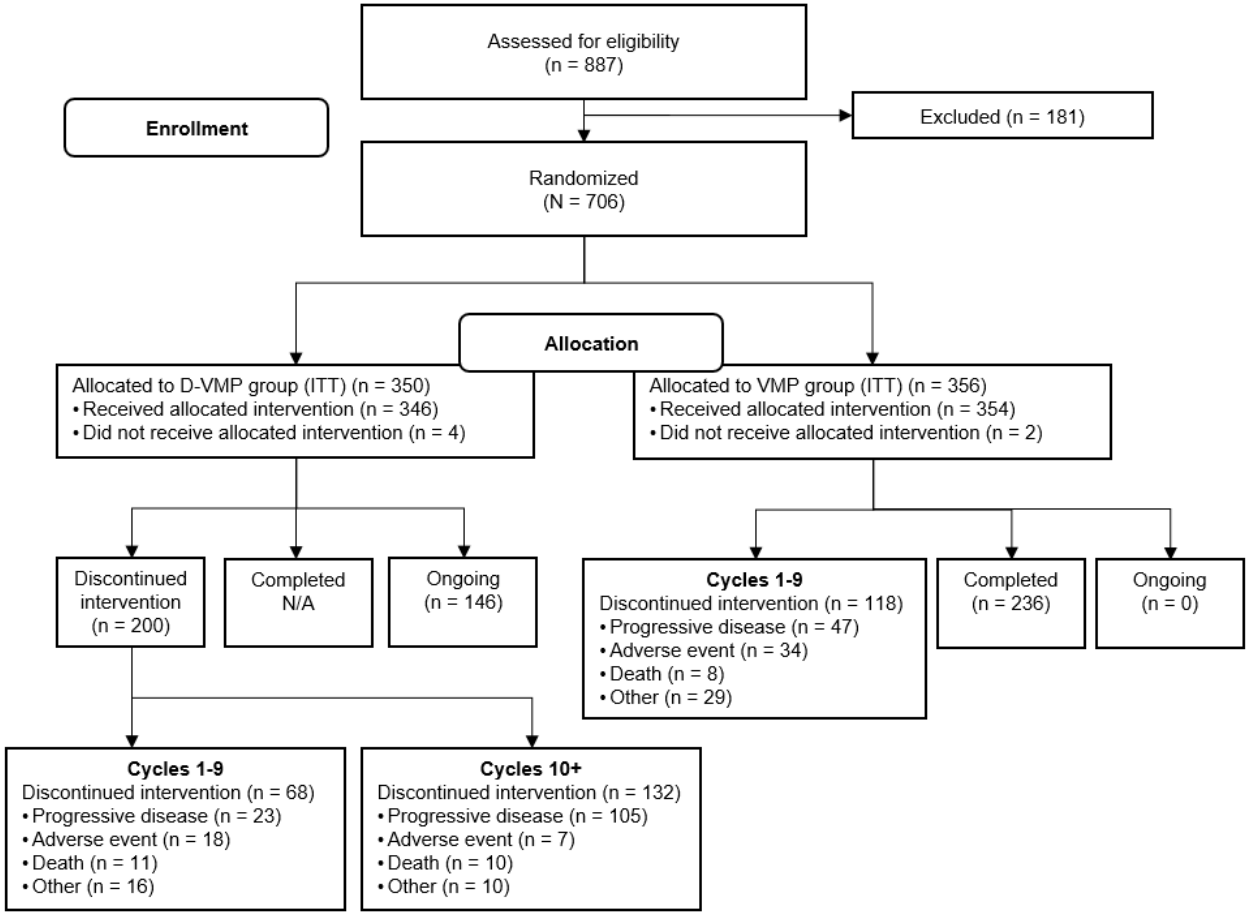
Data are for a univariate and multivariate analysis of combined data from the MAIA and ALCYONE studies evaluating the following variables: MRD-negativity status, age, ISS disease stage, baseline renal function, and cytogenetic risk. MRD-negativity rate was defined as the proportion of patients who achieved ≥CR with negative MRD test results at any time during treatment. A patient was considered MRD positive if MRD negativity was not achieved or if a test was inconclusive or missing, or if they did not reach a best response of ≥CR. No patients were missing data for baseline renal function; patients with missing baseline cytogenetic risk groups (MAIA, n = 95; ALCYONE, n = 90) were excluded from the multivariate model.

Supplemental Figure 1. CONSORT diagrams for MAIA (A) and ALCYONE (B). D-Rd, daratumumab plus lenalidomide/dexamethasone; ITT, intent to treat; Rd, lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

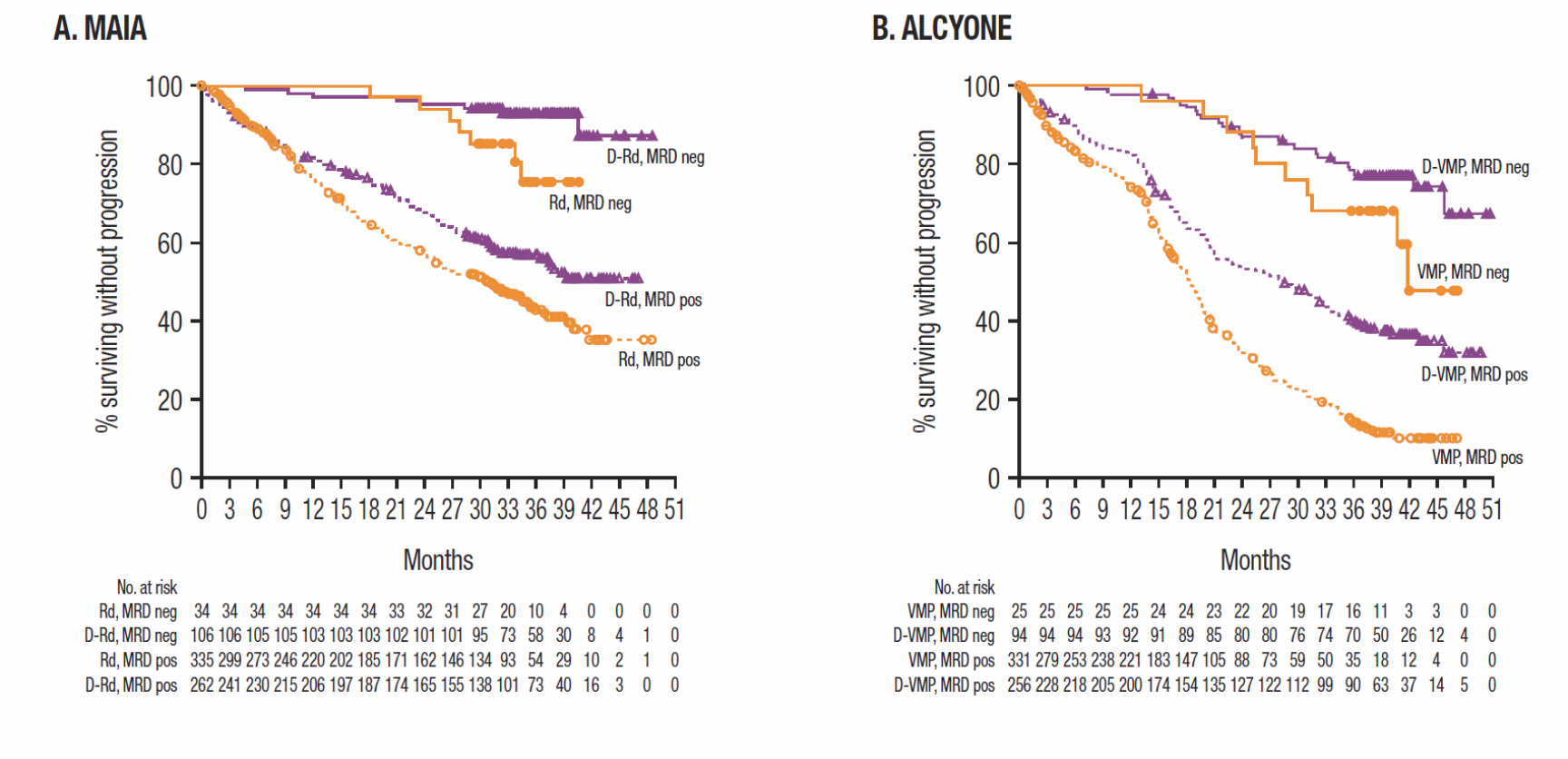
(A) MAIA



(B) ALCYONE[11]

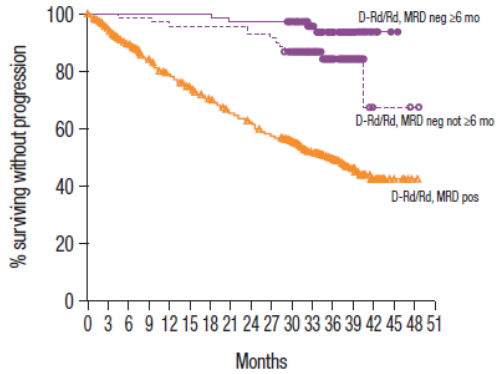

Assessed for eligibility
(n = 887)
Enrollment
Excluded (n = 181)
Randomized
(N = 706)
Allocation
Allocated to D-VMP group (ITT) (n = 350)
• Received allocated intervention (n = 346)
• Did not receive allocated intervention (n = 4)
Allocated to VMP group (ITT) (n = 356)
• Received allocated intervention (n = 354)
• Did not receive allocated intervention (n = 2)
Discontinued intervention (n = 200)
Completed N/A
Ongoing (n = 146)
Cycles 1-9
Discontinued intervention (n = 118)
• Progressive disease (n = 47)
• Adverse event (n = 34)
• Death (n = 8)
• Other (n = 29)
Completed (n = 236)
Ongoing (n = 0)
Cycles 1-9
Discontinued intervention (n = 68)
• Progressive disease (n = 23)
• Adverse event (n = 18)
• Death (n = 11)
• Other (n = 16)
Cycles 10+
Discontinued intervention (n = 132)
• Progressive disease (n = 105)
• Adverse event (n = 7)
• Death (n = 10)
• Other (n = 10)

Supplemental Figure 2. PFS by treatment group based on MRD status (10^{-5}) in MAIA (A) and ALCYONE (B). Shown are Kaplan-Meier estimates of PFS by MRD status among patients in the ITT populations. MRD was assessed at a threshold of 1 tumor cell per 10^5 white blood cells. Purple lines show regimens containing daratumumab (D-Rd and D-VMP); orange lines show standard of care regimens (Rd and VMP). PFS, progression-free survival; MRD, minimal residual disease; ITT, intent to treat; D-Rd, daratumumab plus lenalidomide/dexamethasone. D-VMP, daratumumab plus bortezomib/melphalan/prednisone. MRD, minimal residual disease; Rd, lenalidomide/dexamethasone; VMP, bortezomib/melphalan/prednisone.



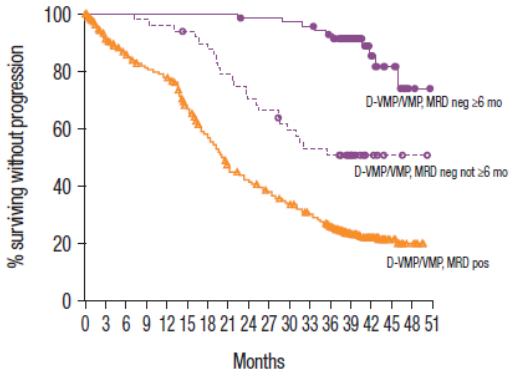
Supplemental Figure 3. PFS based on sustained minimal residual disease (MRD) negativity (10–5; ≥6 months) in MAIA (A), ALCYONE (B), and in both studies pooled (C), and by treatment group for MAIA (D) and ALCYONE (E). Shown are Kaplan-Meier estimates of PFS by sustained MRD negativity lasting ≥6 months among patients in the ITT populations. MRD status was assessed at a threshold of 1 tumor cell per 10^5 white blood cells. Purple lines show MRD-negative patient populations and orange lines show MRD-positive patient populations in panels A-C (D-Rd/Rd shown for MAIA [A]; D-VMP/VMP for ALCYONE [B]; D-Rd/Rd/D-VMP/VMP for all studies combined [C]; purple lines show regimens containing daratumumab (D-Rd for MAIA [D]; and D-VMP for ALCYONE [E]); orange lines show standard of care regimens (Rd for MAIA [D]; VMP for ALCYONE [E]. PFS, progression-free survival; MRD, minimal residual disease; ITT, intent to treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

A. MAIA



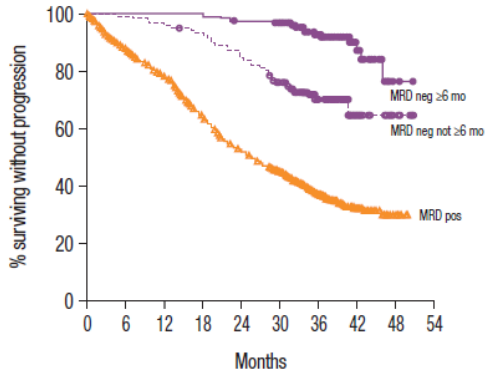
No. at risk																	
D-Rd/Rd, MRD neg ≥6 mo	71	71	71	71	71	71	71	69	69	69	66	54	42	23	6	2	0	0
D-Rd/Rd, MRD neg not ≥6 mo	69	69	68	68	66	66	66	66	64	63	56	39	26	11	2	2	1	0
D-Rd/Rd, MRD pos	597	540	503	461	426	399	372	345	327	301	272	194	127	69	26	5	1	0

B. ALCYONE



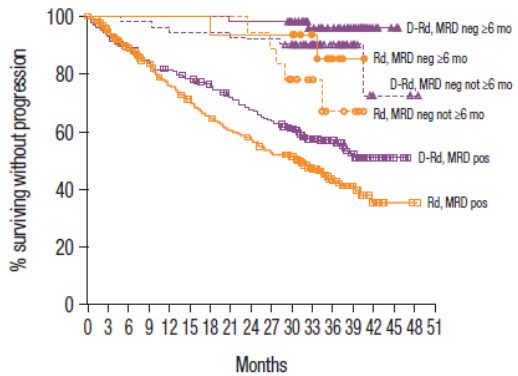
No. at risk																	
D-VMP/VMP, MRD neg ≥6 mo	71	71	71	71	71	71	71	71	69	69	68	67	63	47	23	13	3	0
D-VMP/VMP, MRD neg not ≥6 mo	48	48	48	47	46	44	42	37	33	31	27	24	23	14	6	2	1	0
D-VMP/VMP, MRD pos	587	507	471	443	421	357	301	240	215	195	171	149	125	81	49	18	5	0

C. Pooled



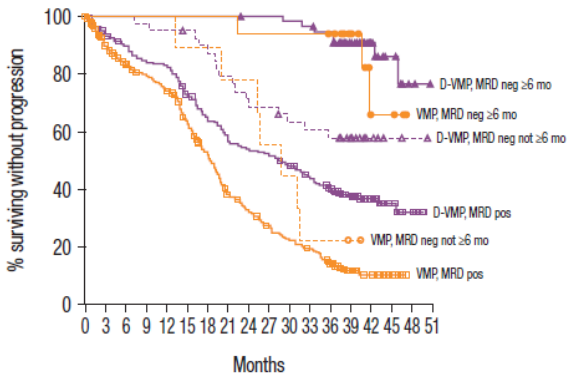
No. at risk										
MRD neg ≥6 mo	142	142	142	142	138	134	105	29	3	0
MRD neg not ≥6 mo	117	116	112	108	97	83	49	8	2	0
MRD pos	1184	974	847	673	542	443	252	75	6	0

D. MAIA



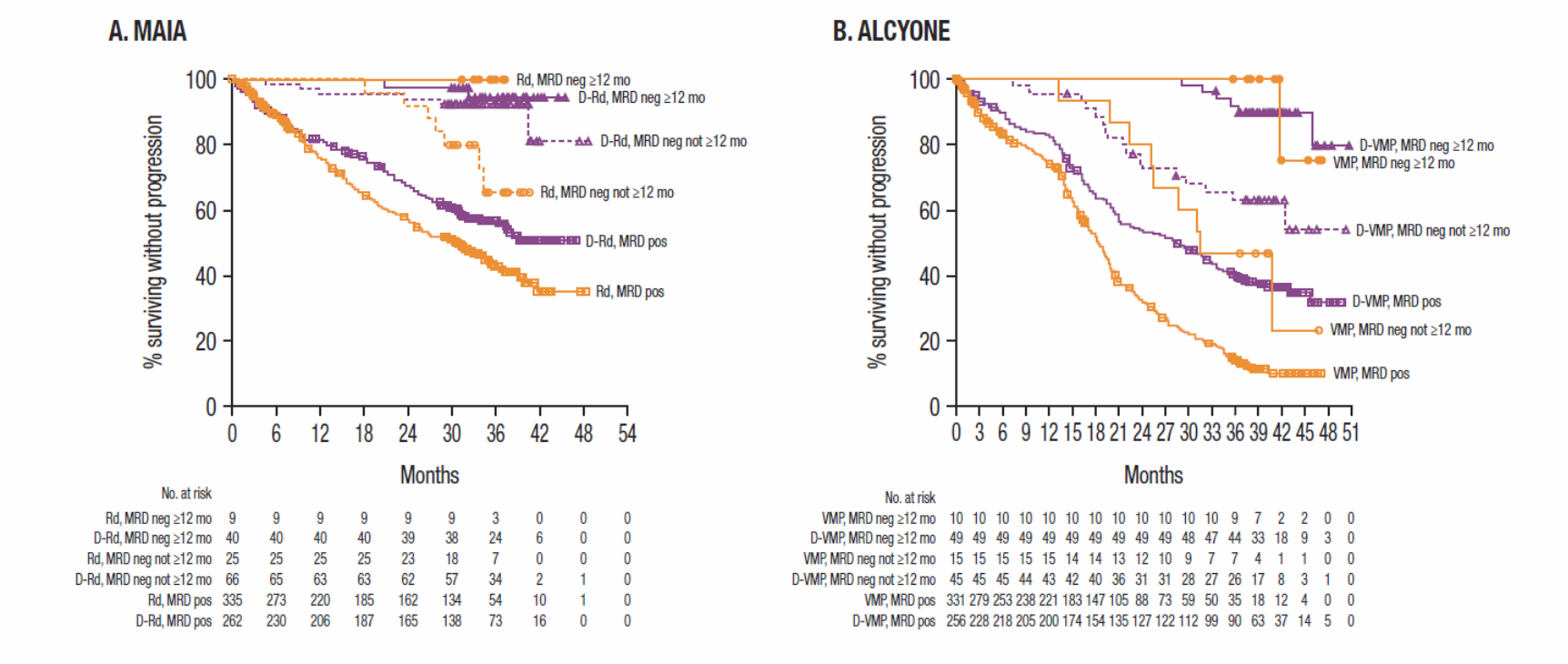
No. at risk																	
Rd, MRD neg ≥6 mo	16	16	16	16	16	16	16	15	15	15	15	11	6	1	0	0	0	0
D-Rd, MRD neg ≥6 mo	55	55	55	55	55	55	55	54	54	54	51	43	36	22	6	2	0	0
Rd, MRD neg not ≥6 mo	18	18	18	18	18	18	18	18	17	16	12	9	4	3	0	0	0	0
D-Rd, MRD neg not ≥6 mo	51	51	50	50	48	48	48	48	47	47	44	30	22	8	2	2	1	0
Rd, MRD pos	335	299	273	246	220	202	185	171	162	146	134	93	54	29	10	2	1	0
D-Rd, MRD pos	262	241	230	215	206	197	187	174	165	155	138	101	73	40	16	3	0	0

E. ALCYONE



No. at risk																	
VMP, MRD neg ≥6 mo	16	16	16	16	16	16	16	16	15	15	15	15	14	10	3	3	0	0
D-VMP, MRD neg ≥6 mo	55	55	55	55	55	55	55	55	54	54	53	52	49	37	20	10	3	0
VMP, MRD neg not ≥6 mo	9	9	9	9	8	8	7	7	5	4	2	2	1	0	0	0	0	0
D-VMP, MRD neg not ≥6 mo	39	39	39	38	37	36	34	30	26	26	23	22	21	13	6	2	1	0
VMP, MRD pos	331	279	253	238	221	183	147	105	88	73	59	50	35	18	12	4	0	0
D-VMP, MRD pos	256	228	218	205	200	174	154	135	127	122	112	99	90	63	37	14	5	0

Supplemental Figure 4. PFS by treatment group based on sustained MRD negativity (10^{-5}; ≥12 months) in MAIA (A) and ALCYONE (B). Shown are Kaplan-Meier estimates of PFS by sustained MRD negativity lasting ≥12 months among patients in the ITT populations. MRD status was assessed at a threshold of 1 tumor cell per 10^5 white blood cells. Purple lines show regimens containing daratumumab (D-Rd and D-VMP); orange lines show standard of care regimens (Rd and VMP). PFS for patients with sustained MRD negativity lasting ≥12 months was previously reported for ALCYONE.[11] PFS, progression-free survival; MRD, minimal residual disease; ITT, intent to treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; Rd, lenalidomide/dexamethasone; VMP, bortezomib/melphalan/prednisone.



Supplemental Figure 5. PFS based on sustained MRD (10^{-5}) negativity lasting ≥6 months (A) or ≥12 months (B) in the pooled daratumumab-based combination groups (D-Rd/D-VMP) versus the pooled control groups (Rd/VMP) in MAIA and ALCYONE. Shown are the results of the Kaplan-Meier estimates of PFS among patients in the ITT population based on the absence of MRD at a threshold of 1 tumor cell per 10^5 white blood cells or on sustained MRD negativity at ≥6 or ≥12 months at a threshold of 1 tumor cell per 10^5 white blood cells. PFS, progression-free survival; MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; Rd, lenalidomide/dexamethasone; VMP, bortezomib/melphalan/prednisone; ITT, intent to treat.