**Supplemental Appendix**

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

Supplement to: Cavo M, San-Miguel J, Usmani SZ, et al. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, MAIA

**Supplemental Table 1. Patients with high cytogenetic risk who achieved ≥CR with MRD negativity by treatment group within each study**

| | POLLUX | | | CASTOR | | |
|---|---|---|---|---|---|---|
| **Patients, n (%)** | **D-Rd** | **Rd** | **Total** | **D-Vd** | **Vd** | **Total** |
| High cytogenetic risk | n = 35 | n = 35 | n = 70 | n = 40 | n = 35 | n = 75 |
| ≥CR and MRD negative | 10 (28.6) | 1 (2.9) | 11 (15.7) | 6 (15.0) | 0 | 6 (8.0) |

| | ALCYONE | | | MAIA | | |
|---|---|---|---|---|---|---|
| **Patients, n (%)** | **D-VMP** | **VMP** | **Total** | **D-Rd** | **Rd** | **Total** |
| High cytogenetic risk | n = 53 | n = 45 | n = 98 | n = 48 | n = 44 | n = 92 |
| ≥CR and MRD negative | 14 (26.4) | 4 (8.9) | 18 (18.4) | 11 (22.9) | 1 (2.3) | 12 (13.0) |

CR, complete response; MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide and dexamethasone; D-Vd, daratumumab plus bortezomib/dexamethasone; Vd, bortezomib and dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, prednisone.

**Supplemental Table 2. Time-varying Cox proportional hazard model for PFS2***

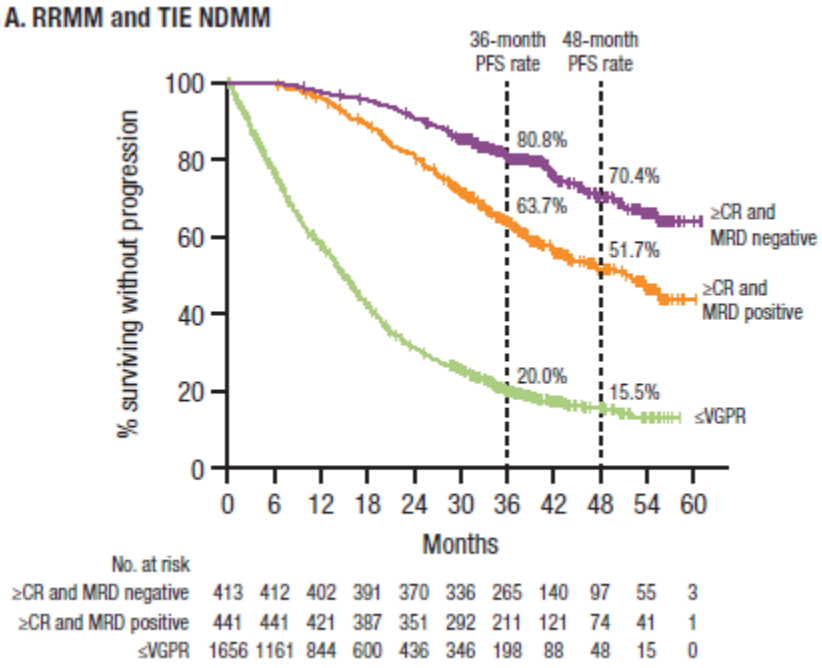
| Variable | HR (95% CI) | *P* value |
|---|---|---|
| **RRMM and TIE NDMM** | | |
| ***Univariate Analysis*** | | |
| Response group (≥CR + $MRD^-$ vs ≤VGPR or $MRD^+$) | 0.22 (0.15-0.32) | < .0001 |
| ***Multivariate Analysis*** | | |
| Response group (≥CR + $MRD^-$ vs ≤VGPR or $MRD^+$) | 0.23 (0.16-0.34) | < .0001 |
| Age | 0.99 (0.98-0.99) | .001 |
| ISS disease stage (II vs I) | 1.47 (1.24-1.74) | < .0001 |
| ISS disease stage (III vs I) | 1.73 (1.44-2.09) | < .0001 |
| Baseline renal function (>60 mL/min vs ≤60 mL/min) | 0.95 (0.82-1.11) | .56 |
| Cytogenetic risk (high vs standard) | 1.51 (1.26-1.81) | < .0001 |
| **RRMM ≤2PL and TIE NDMM** | | |
| ***Univariate Analysis*** | | |
| Response group (≥CR + $MRD^-$ vs ≤VGPR or $MRD^+$) | 0.21 (0.14-0.32) | < .0001 |
| ***Multivariate Analysis*** | | |
| Response group (≥CR + $MRD^-$ vs ≤VGPR or $MRD^+$) | 0.23 (0.15-0.35) | < .0001 |
| Age | 0.99 (0.98-1.00) | .021 |
| ISS disease stage (II vs I) | 1.51 (1.25-1.81) | < .0001 |
| ISS disease stage (III vs I) | 1.75 (1.43-2.14) | < .0001 |
| Baseline renal function (>60 mL/min vs ≤60 mL/min) | 0.99 (0.84-1.17) | .90 |
| Cytogenetic risk (high vs standard) | 1.55 (1.29-1.88) | < .0001 |

*Data are shown for univariate and multivariate analyses using combined data from all RRMM and TIE NDMM patients in POLLUX, CASTOR, ALCYONE, and MAIA (RRMM and TIE NDMM); and among patients with RRMM with ≤2 prior lines of therapy from POLLUX and CASTOR and TIE NDMM from ALCYONE and MAIA (RRMM ≤2PL and TIE NDMM). The following variables were evaluated: MRD negativity status with best response, age, ISS disease stage, baseline renal function, and cytogenetic risk. Data with missing baseline renal function groups or cytogenetic risk groups are excluded from the multivariate model. RRMM and TIE NDMM patients with missing data for baseline renal function (POLLUX, n = 9; CASTOR, n = 20; ALCYONE, n = 0; MAIA, n = 0; Total = 29) or cytogenetic risk (POLLUX, n = 130; CASTOR, n = 142; ALCYONE, n = 90; MAIA, n = 95; Total = 457) were excluded from the multivariate model. RRMM ≤2PL and TIE NDMM patients with missing data for baseline renal function (POLLUX, n = 8; CASTOR, n = 14; ALCYONE, n = 0; MAIA, n = 0; Total = 22) or cytogenetic risk (POLLUX, n = 108; CASTOR, n = 111; ALCYONE, n = 90; MAIA, n = 95; Total = 404) were excluded from the multivariate model.

PFS2, progression-free survival on next subsequent therapy; CI, confidence interval; RRMM, relapsed/refractory multiple myeloma; TIE NDMM, transplant ineligible newly diagnosed

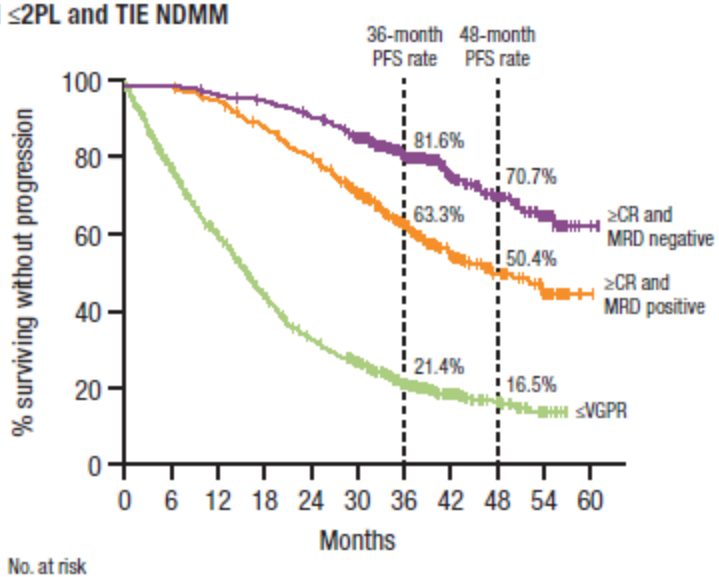
multiple myeloma; CR, complete response; MRD, minimal residual disease; VGPR, very good partial response; ISS, international staging system; PL, prior lines of therapy.

**Supplemental Figure 1. PFS by response and MRD status ($10^{-5}$) among patients who achieved complete response or better and were MRD negative (≥CR and MRD negative), or who achieved complete response or better and were MRD positive (≥CR and MRD positive), or who achieved a response less than complete response (≤VGPR) for patients pooled from POLLUX, CASTOR, ALCYONE, and MAIA (A); and for patients in POLLUX and CASTOR with ≤2PL pooled with all patients from ALCYONE and MAIA (B).** Shown are Kaplan-Meier estimates of PFS among patients in the intention-to-treat population based on the absence of MRD as measured using the threshold of one tumor cell per $10^5$ white cells and response categories according to IMWG criteria. PFS, progression-free survival; MRD, minimal residual disease; CR, complete response; VGPR, very good partial response; ≤2PL, ≤2 prior lines of therapy; RRMM, relapsed/refractory multiple myeloma; TIE NDMM, transplant-ineligible newly diagnosed multiple myeloma; IMWG, International Myeloma Working Group.




| Groups | HR (95% CI) | p value |
|---|---|---|
| ≥CR and MRD negative vs ≥CR and MRD positive | 0.52 (0.41–0.66) | <0.0001 |
| ≥CR and MRD negative vs ≤VGPR | 0.14 (0.11–0.17) | <0.0001 |
| ≥CR and MRD positive vs ≤VGPR | 0.27 (0.23–0.31) | <0.0001 |

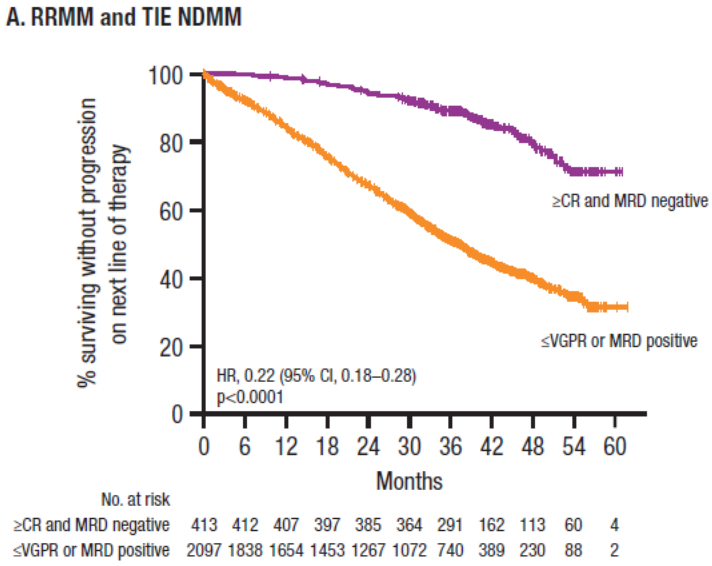
**B. RRMM ≤2PL and TIE NDMM**

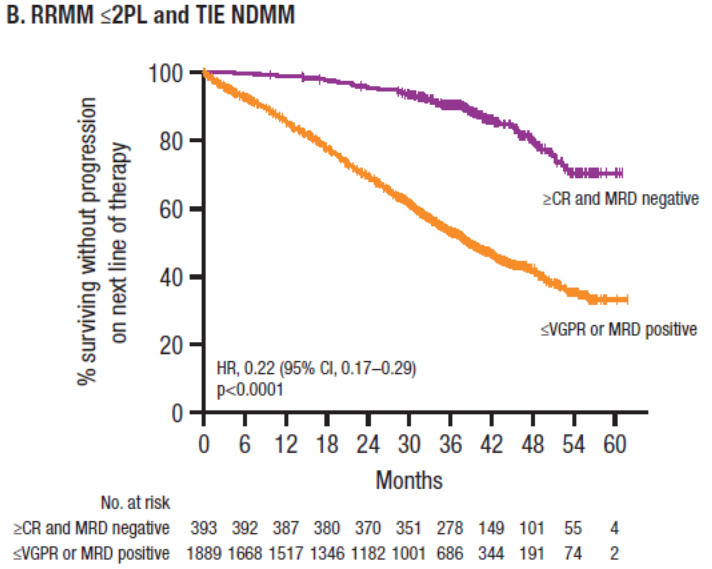



| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥CR and MRD negative | 393 | 392 | 383 | 374 | 356 | 323 | 252 | 127 | 86 | 50 | 3 |
| ≥CR and MRD positive | 419 | 419 | 401 | 369 | 336 | 278 | 197 | 108 | 61 | 36 | 1 |
| ≤VGPR | 1470 | 1052 | 786 | 564 | 411 | 325 | 185 | 78 | 40 | 10 | 0 |

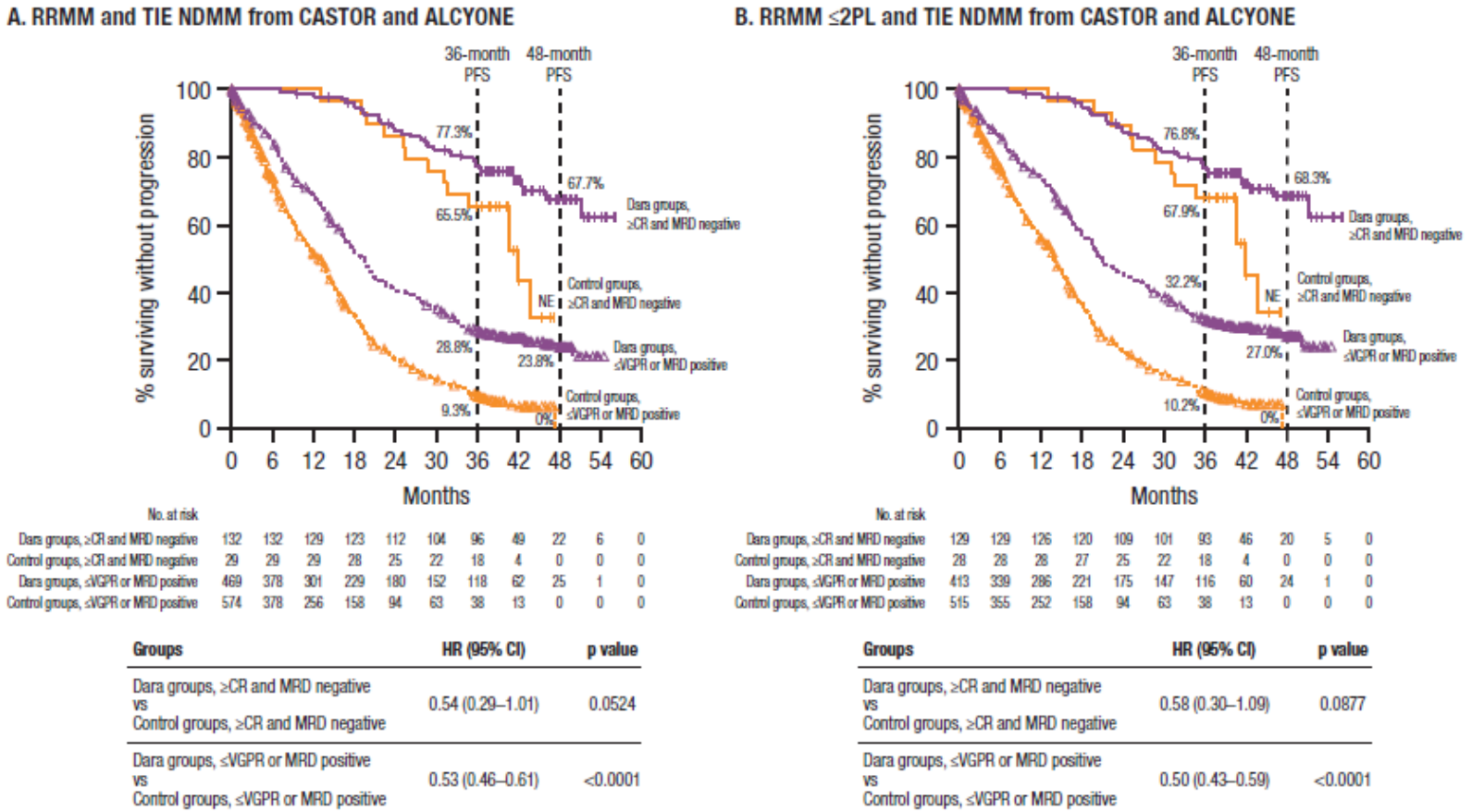
| Groups | HR (95% CI) | p value |
|---|---|---|
| ≥CR and MRD negative vs ≥CR and MRD positive | 0.50 (0.39–0.64) | <0.0001 |
| ≥CR and MRD negative vs ≤VGPR | 0.14 (0.11–0.17) | <0.0001 |
| ≥CR and MRD positive vs ≤VGPR | 0.28 (0.24–0.33) | <0.0001 |

**Supplemental Figure 2. PFS2 by response and MRD status ($10^{-5}$) among patients who achieved complete response or better and were MRD negative (≥CR and MRD negative) or who achieved a response less than complete response or were MRD positive (≤VGPR or MRD positive) for patients pooled from POLLUX, CASTOR, ALCYONE, and MAIA (A); and for patients in POLLUX and CASTOR with ≤2PL pooled with all patients from ALCYONE and MAIA (B).** Shown are Kaplan-Meier estimates of PFS2 among patients in the ITT population based on the absence of MRD as measured using the threshold of one tumor cell per $10^5$ white cells and response categories according to IMWG criteria. PFS2, progression-free survival on next subsequent therapy; MRD, minimal residual disease; CR, complete response; VGPR, very good partial response; ≤2PL, ≤2 prior lines of therapy; RRMM, relapsed/refractory multiple myeloma; TIE NDMM, transplant-ineligible newly diagnosed multiple myeloma; HR, hazard ratio; CI, confidence interval; ITT, intention-to-treat; IMWG, International Myeloma Working Group.



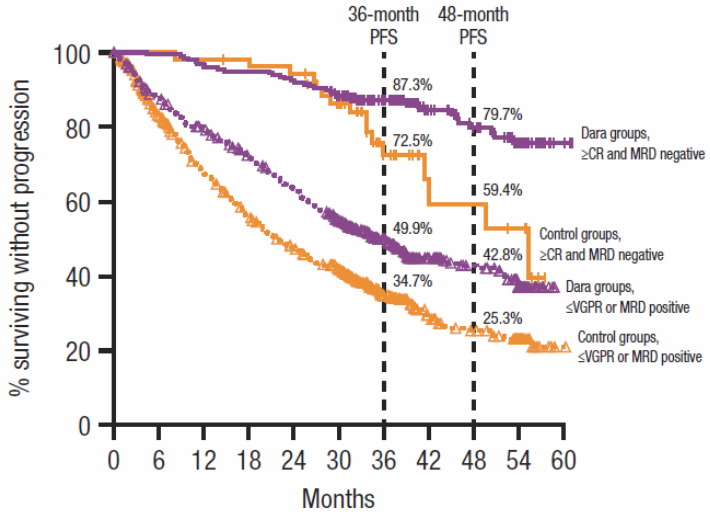
**Supplemental Figure 3. PFS by response and MRD status ($10^{-5}$) among patients in the pooled daratumumab combination groups versus the pooled control groups including patients in CASTOR and ALCYONE in which standard of care was given for a fixed number of cycles and daratumumab was given until progression (A, B), or patients in POLLUX and MAIA in which study therapies were given until disease progression or unacceptable toxicity (C, D) for all patients combined (A, C) or for patients in POLLUX and CASTOR with ≤2PL pooled with all patients from ALCYONE and MAIA (B, D).** Shown are Kaplan-Meier estimates of PFS among patients in the intention-to-treat population based on the absence of MRD as measured using the threshold of one tumor cell per $10^5$ white cells and response categories according to IMWG criteria. PFS, progression-free survival; MRD, minimal residual disease; ≤2PL, ≤2 prior lines of therapy; RRMM, relapsed/refractory multiple myeloma; TIE NDMM, transplant-ineligible newly diagnosed multiple myeloma; CR, complete response; VGPR, very good partial response; Dara, daratumumab; IMWG, International Myeloma Working Group.




| Groups | HR (95% CI) | p value |
|---|---|---|
| Dara groups, ≥CR and MRD negative vs Control groups, ≥CR and MRD negative | 0.54 (0.29–1.01) | 0.0524 |
| Dara groups, ≤VGPR or MRD positive vs Control groups, ≤VGPR or MRD positive | 0.53 (0.46–0.61) | <0.0001 |

| Groups | HR (95% CI) | p value |
|---|---|---|
| Dara groups, ≥CR and MRD negative vs Control groups, ≥CR and MRD negative | 0.58 (0.30–1.09) | 0.0877 |
| Dara groups, ≤VGPR or MRD positive vs Control groups, ≤VGPR or MRD positive | 0.50 (0.43–0.59) | <0.0001 |

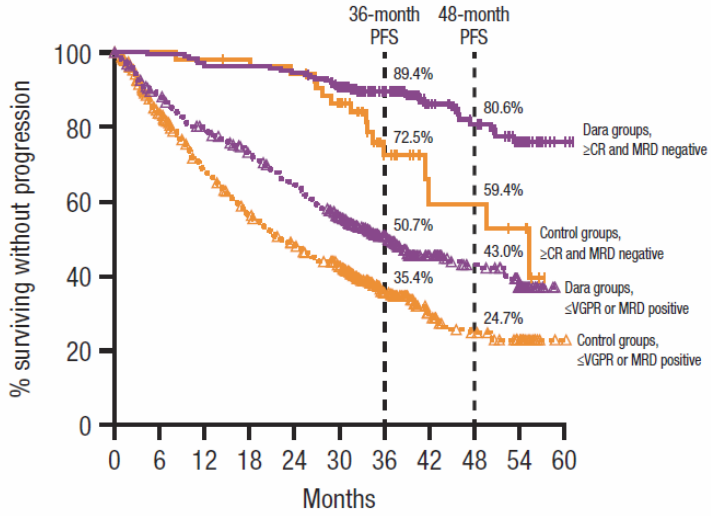
## C. RRMM and TIE NDMM from POLLUX and MAIA




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dara groups, ≥CR and MRD negative | 199 | 198 | 192 | 189 | 184 | 169 | 130 | 78 | 66 | 42 | 3 |
| Control groups, ≥CR and MRD negative | 53 | 53 | 52 | 51 | 49 | 41 | 21 | 9 | 9 | 7 | 0 |
| Dara groups, ≤VGPR or MRD positive | 455 | 386 | 346 | 305 | 266 | 220 | 144 | 80 | 60 | 34 | 0 |
| Control groups, ≤VGPR or MRD positive | 599 | 460 | 362 | 295 | 247 | 203 | 109 | 54 | 37 | 21 | 1 |

| Groups | HR (95% CI) | p value |
|---|---|---|
| Dara groups, ≥CR and MRD negative vs Control groups, ≥CR and MRD negative | 0.52 (0.29–0.94) | 0.0317 |
| Dara groups, ≤VGPR or MRD positive vs Control groups, ≤VGPR or MRD positive | 0.65 (0.55–0.77) | <0.0001 |

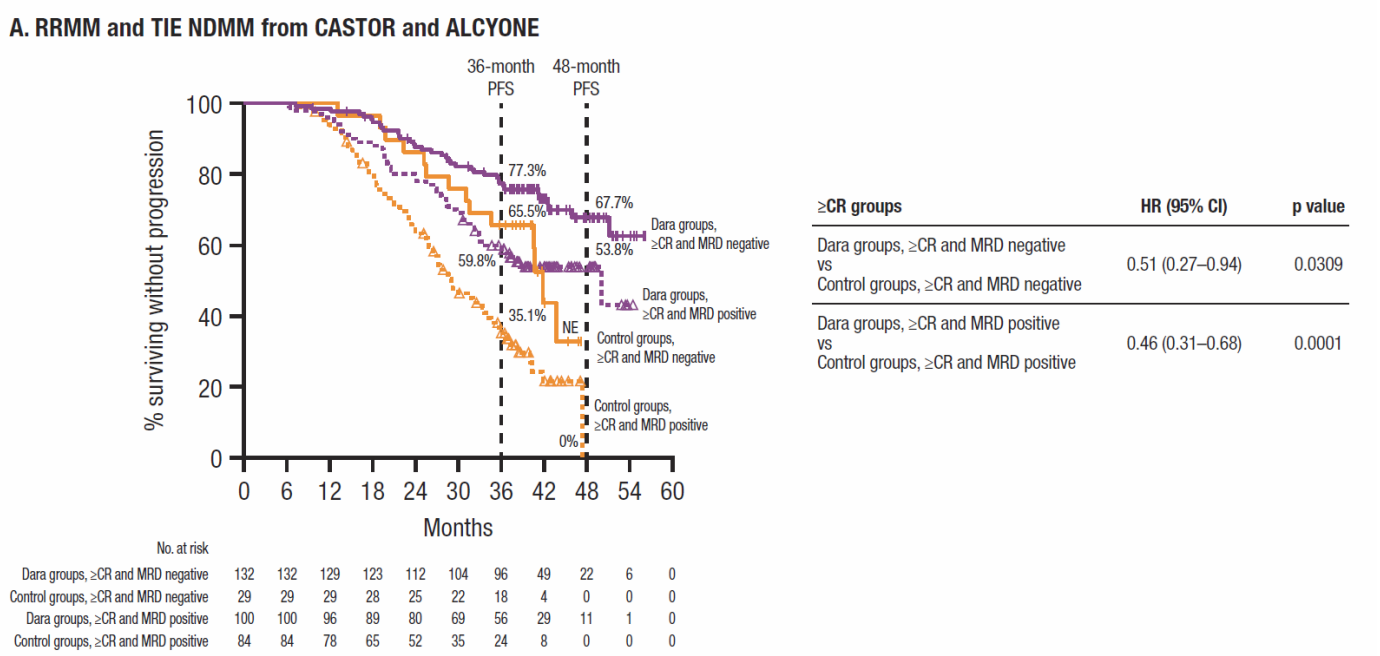
## D. RRMM ≤2PL and TIE NDMM from POLLUX and MAIA




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dara groups, ≥CR and MRD negative | 183 | 182 | 177 | 176 | 173 | 159 | 120 | 68 | 57 | 38 | 3 |
| Control groups, ≥CR and MRD negative | 53 | 53 | 52 | 51 | 49 | 41 | 21 | 9 | 9 | 7 | 0 |
| Dara groups, ≤VGPR or MRD positive | 419 | 359 | 321 | 286 | 251 | 207 | 132 | 69 | 49 | 29 | 0 |
| Control groups, ≤VGPR or MRD positive | 542 | 418 | 328 | 268 | 227 | 186 | 96 | 44 | 28 | 16 | 1 |

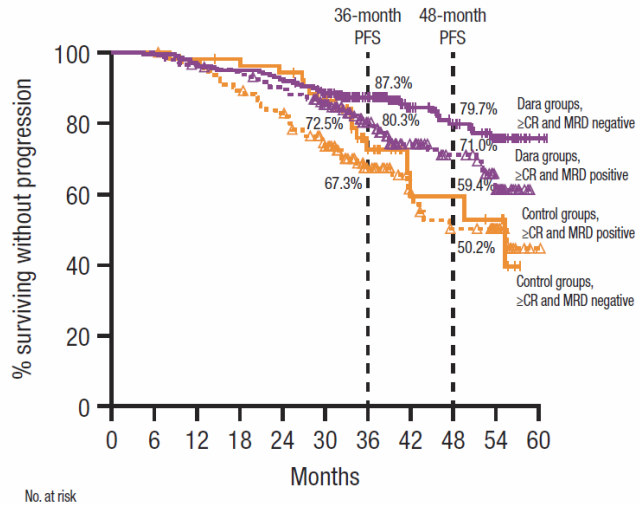
| Groups | HR (95% CI) | p value |
|---|---|---|
| Dara groups, ≥CR and MRD negative vs Control groups, ≥CR and MRD negative | 0.47 (0.25–0.86) | 0.0145 |
| Dara groups, ≤VGPR or MRD positive vs Control groups, ≤VGPR or MRD positive | 0.65 (0.55–0.77) | <0.0001 |

**Supplemental Figure 4. PFS by MRD status ($10^{-5}$) among all patients who achieved complete response or better in the pooled daratumumab combination groups versus the pooled control groups from patients CASTOR and ALCYONE in which standard of care was given for a fixed number of cycles and daratumumab was given until progression (A), or from patients in POLLUX and MAIA in which study therapies were given until disease progression or unacceptable toxicity (B).** Shown are Kaplan-Meier estimates of PFS among patients in the intention-to-treat population based on the absence of MRD as measured using the threshold of one tumor cell per $10^5$ white cells and response categories according to IMWG criteria. PFS, progression-free survival; MRD, minimal residual disease; RRMM, relapsed/refractory multiple myeloma; TIE NDMM, transplant ineligible newly diagnosed multiple myeloma; Dara, daratumumab; CR, complete response; HR, hazard ratio; CI, confidence interval.




| ≥CR groups | HR (95% CI) | p value |
|---|---|---|
| Dara groups, ≥CR and MRD negative vs Control groups, ≥CR and MRD negative | 0.51 (0.27–0.94) | 0.0309 |
| Dara groups, ≥CR and MRD positive vs Control groups, ≥CR and MRD positive | 0.46 (0.31–0.68) | 0.0001 |

**B. RRMM and TIE NDMM from POLLUX and MAIA**




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dara groups, ≥CR and MRD negative | 199 | 198 | 192 | 189 | 184 | 169 | 130 | 78 | 66 | 42 | 3 |
| Control groups, ≥CR and MRD negative | 53 | 53 | 52 | 51 | 49 | 41 | 21 | 9 | 9 | 7 | 0 |
| Dara groups, ≥CR and MRD positive | 145 | 145 | 139 | 134 | 128 | 115 | 86 | 56 | 43 | 26 | 0 |
| Control groups, ≥CR and MRD positive | 112 | 112 | 108 | 99 | 91 | 73 | 45 | 28 | 20 | 14 | 1 |

| ≥CR groups | HR (95% CI) | p value |
|---|---|---|
| Dara groups, ≥CR and MRD negative vs Control groups, ≥CR and MRD negative | 0.48 (0.26–0.87) | 0.0152 |
| Dara groups, ≥CR and MRD positive vs Control groups, ≥CR and MRD positive | 0.60 (0.39–0.92) | 0.0200 |