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Sustained Minimal Residual Disease Negativity With Daratumumab in Newly Diagnosed Multiple Myeloma: MAIA and ALCYONE

Short title: MRD negativity in NDMM from MAIA and ALCYONE

Jesus San-Miguel,[1] Hervé Avet-Loiseau,[2] Bruno Paiva,[1] Shaji Kumar,[3] Meletios A. Dimopoulos,[4] Thierry Facon,[5] María-Victoria Mateos,[6] Cyrille Touzeau,[7] Andrzej Jakubowiak,[8] Saad Z. Usmani,[9] Gordon Cook,[10] Michele Cavo,[11] Hang Quach,[12] Jon Ukropec,[13,*] Priya Ramaswami,[14] Huiling Pei,[14] Mia Qi,[15] Steven Sun,[15] Jianping Wang,[15] Maria Krevvata,[16] Nikki DeAngelis,[16] Christoph Heuck,[16] Rian Van Rampelbergh,[17] Anupa Kudva,[15] Rachel Kobos,[15] Ming Qi,[16] Nizar J. Bahlis[18]

[1]Clínica Universidad de Navarra, Centro de Investigación Médica Aplicada (CIMA), Instituto de Investigación Sanitaria de Navarra, (IDISNA), CIBER-ONC number CB16/12/00369, Pamplona, Spain; [2]Unite de Genomique du Myelome, IUC-Oncopole, Toulouse, France; [3]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [4]National and Kapodistrian University of Athens, Athens, Greece; [5]University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France; [6]University Hospital of Salamanca/IBSAL/Cancer Research Center- IBMCC (USAL-CSIC), Salamanca, Spain; [7]Hematology, University Hospital Hôtel-Dieu, Nantes, France; [8]University of Chicago Medical Center, Chicago, IL, USA; [9]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [10]Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust and University of Leeds, Leeds, UK; [11]Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [12]University of Melbourne, St. Vincent's

Hospital, Melbourne, Australia; [13]Janssen Global Medical Affairs, Horsham, PA, USA; [14]Janssen Research & Development, LLC, Titusville, NJ, USA; [15]Janssen Research & Development, LLC, Raritan, NJ, USA; [16]Janssen Research & Development, LLC, Spring House, PA, USA; [17]Janssen Research & Development, Beerse, Belgium; [18]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, Alberta, Canada.

[*]At the time of the study.

Corresponding author:

Jesus San-Miguel, MD

Clínica Universidad de Navarra, Centro de Investigación Médica Aplicada (CIMA), Instituto de Investigación Sanitaria de Navarra (IDISNA), CIBER-ONC number CB16/12/00369

Av. de Pío XII, 55, 31008 Pamplona, Navarra, Spain

Email: sanmiguel@unav.es

Tel: 34 948 296 296

Fax: 34 948 296 500

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Key points:

- In patients with transplant-ineligible NDMM, durable MRD negativity is associated with improved PFS
- Daratumumab-based therapies are associated with higher rates and durability of MRD negativity

Abstract

In patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM), daratumumab reduced the risk of disease progression or death by 44% in MAIA (daratumumab/lenalidomide/dexamethasone; D-Rd) and 58% in ALCYONE (daratumumab/bortezomib/melphalan/prednisone; D-VMP). Minimal residual disease (MRD) is a sensitive measure of disease and response to therapy. MRD-negativity status and durability were assessed in MAIA and ALCYONE. MRD assessments using next-generation sequencing (10^{-5}) occurred for patients achieving complete response (CR) or better, and after ≥CR at 12, 18, 24, and 30 months from the first dose. Progression-free survival (PFS) by MRD status and sustained MRD negativity lasting ≥6 and ≥12 months were analyzed in the intent-to-treat population and among patients achieving ≥CR. In MAIA, (D-Rd, n=368; Rd, n=369), and ALCYONE (D-VMP, n=350; VMP, n=356), the median duration of follow-up was 36.4 months and 40.1 months, respectively. MRD-negative status and sustained MRD negativity lasting ≥6 and ≥12 months were associated with improved PFS, regardless of treatment group. However, daratumumab-based therapy improved rates of MRD negativity lasting ≥6 months (D-Rd, 14.9% vs Rd, 4.3%; D-VMP, 15.7% vs VMP, 4.5%) and ≥12 months (D-Rd, 10.9% vs Rd, 2.4%; D-VMP, 14.0% vs VMP, 2.8%), both of which translated to improved PFS versus control groups. In a pooled analysis, patients who achieved ≥CR and were MRD negative had improved PFS versus patients who did not achieve CR or were MRD positive. Patients with NDMM who achieved sustained MRD negativity or MRD negativity with ≥CR had deep remission and improved clinical outcomes. ClinicalTrials.gov identifier NCT02252172 (MAIA); NCT02195479 (ALCYONE).

Introduction

Among patients with newly diagnosed multiple myeloma (NDMM), recent treatment advancements have improved long-term outcomes. However, with these improvements come unique challenges as clinicians evaluate the efficacy of emerging therapies. Specifically, the duration until read-out of clinical trials is long for traditionally used endpoints such as progression-free survival (PFS) and overall survival (OS), resulting in increased time until novel therapies are translated into clinical practice. Therefore, new disease assessment methods are needed that could serve as surrogate endpoints with more expedient read-out.

Minimal residual disease (MRD) is a sensitive measure of tumor cells in bone marrow that reflects remission status. Many studies have demonstrated that MRD-negative status is indicative of a deep response to therapy that is associated with improved PFS and OS.[1-11] While PFS and OS remain key outcomes in clinical studies, MRD status is being explored as a co-primary endpoint in clinical trials for multiple myeloma.[9] Importantly, however, several aspects of MRD assessment require optimization and standardization, including patient selection, timing of assessment, sensitivity thresholds, frequency of monitoring, and testing methodologies.[12] To this end, the International Myeloma Working Group (IMWG) criteria for assessing MRD negativity state that patients must achieve a complete response or better (≥CR) and MRD-negative status, with a minimum sensitivity of 1 nucleated tumor cell in 100,000 normal cells (a 10^{-5} threshold) either by next-generation sequencing or next-generation flow cytometry.[13]

Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor[14-17] and immunomodulatory[18-20] mechanism of action. Daratumumab is approved across multiple

lines of therapy for multiple myeloma;[21] daratumumab-based regimens consistently improve rates of MRD negativity as well as long-term outcomes such as PFS and OS relative to standard of care. Two phase 3 clinical studies, MAIA and ALCYONE, have evaluated daratumumab-based regimens for patients with transplant-ineligible NDMM.

In the primary analysis of MAIA with 28.0 months of median follow-up, daratumumab plus lenalidomide and dexamethasone (D-Rd) reduced the risk of disease progression or death by 44% compared with the control group (lenalidomide and dexamethasone; Rd). Additionally, more D-Rd patients achieved MRD negativity compared with those who received Rd (24% vs 7%; $P \leq 0.001$).[10] With longer follow-up of MAIA (36.4 months), D-Rd versus Rd continued to improve clinical outcomes and also demonstrated improved MRD durability lasting ≥6 months (15% vs 4%; $P < 0.0001$) and ≥12 months (11% vs 2%; $P < 0.0001$).[22] In the primary analysis of ALCYONE, daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) reduced the risk of disease progression or death by 50% with 16.5 months of median follow-up compared with the control group (bortezomib, melphalan, and prednisone; VMP).[23] In support of the primary endpoint, the MRD-negativity rate at that time was also improved for D-VMP versus VMP (22% vs 6%; $P < 0.001$). With longer follow-up of ALCYONE (40.1 months), the clinical benefit of D-VMP was maintained; importantly, D-VMP reduced the risk of death by 40% compared with VMP ($P = 0.0003$). At the time of this longer follow-up, more patients who received D-VMP versus VMP achieved durable MRD negativity lasting ≥6 months (16% vs 5%; $P < 0.0001$) and ≥12 months (14% vs 3%; $P < 0.0001$).[11] Both MAIA and ALCYONE demonstrated that daratumumab-based regimens improved outcomes compared with standard of

care; in addition, they also demonstrated that achievement of MRD negativity was associated with longer PFS, irrespective of trial treatments.

Here we provide an evaluation of sustained MRD negativity in patients with transplant-ineligible NDMM; while the benefit of achieving MRD negativity has been well established, this study is the first to assess the prognostic value of sustained MRD negativity lasting ≥6 or ≥12 months in NDMM. Specifically, we present an analysis of the association of MRD durability with PFS using data from the phase 3 MAIA and ALCYONE studies after 36.4 months and 40.1 months of median follow-up, respectively. These data support the use of MRD durability as a predictive and prognostic tool in NDMM and provide context for the length of MRD durability that is clinically meaningful.

Methods

Trial Design and Oversight

The study designs of the phase 3 randomized, open-label, multicenter MAIA (ClinicalTrials.gov Identifier: NCT02252172)[10] and ALCYONE (NCT02195479)[23] studies have been published previously with the primary endpoint analyses for each study. Briefly, MAIA and ALCYONE evaluated daratumumab plus Rd or VMP, respectively, in patients with transplant-ineligible NDMM. In both studies, patients had documented measurable disease according to IMWG criteria[24] and were ineligible for high-dose chemotherapy or stem cell transplantation due to age (≥65 years) or unacceptable coexisting conditions. All patients provided written informed consent, and the studies were approved by independent ethics committees/institutional review

boards and conducted in accordance with the Declaration of Helsinki and current International Conference on Harmonisation Good Clinical Practice guidelines.

Randomization and Study Treatment

In each study, patients were randomized (1:1) to each treatment group based on stratification factors (International Staging System [ISS] disease stage [I vs II vs III, with higher stages indicating a poorer prognosis], geographic region [North America vs other for MAIA; Europe vs other for ALCYONE], and age [<75 years vs ≥75 years]).[10,23] In MAIA, all patients received lenalidomide (25 mg orally on Days 1-21) and dexamethasone (40 mg weekly) during each 28-day cycle. Patients in the D-Rd group received daratumumab (16 mg/kg) weekly for Cycles 1-2, every other week for Cycles 3-6, and every 4 weeks thereafter. Study treatment continued until progressive disease or unacceptable toxicity. In ALCYONE, all patients received up to nine 42-day cycles of bortezomib (1.3 mg/m^2 subcutaneously twice weekly during Weeks 1, 2, 4, and 5 of Cycle 1, and once weekly during Weeks 1, 2, 4, and 5 of Cycles 2-9), melphalan (9 mg/m^2 orally on Days 1-4 of each cycle), and prednisone (60 mg/m^2 orally on Days 1-4 of each cycle). In the D-VMP group, patients received daratumumab (16 mg/kg intravenously) weekly in Cycle 1, every 3 weeks in Cycles 2-9, and every 4 weeks thereafter until disease progression or unacceptable toxicity. For each study, pre- and post-infusion medications as well as dose modifications have been previously described.[10,23]

Endpoints and Assessments

For MAIA and ALCYONE, the primary endpoint was PFS and was reported previously.[10,23] Response assessments and disease assessments were conducted using a central laboratory and a validated computer algorithm according to IMWG criteria.[13,25,26] MRD assessments were to occur for all patients who achieved ≥CR. For patients who achieved ≥CR, additional MRD assessments occurred at 12, 18, 24, and 30 months after the first dose. MRD was assessed from bone marrow aspirates and evaluated with next-generation sequencing using the clonoSEQ® assay (v.2.0; Adaptive Biotechnologies, Seattle, WA),[27] according to IMWG criteria.[13] MRD-negativity rate was defined as the proportion of patients with negative MRD test results at any time during treatment. A minimum cell input equivalent to the given sensitivity threshold was required to determine MRD negativity (eg, MRD at 10^{-5} required that ≥100,000 cells were evaluated). A patient was considered MRD positive if MRD negativity was not achieved or if a test was inconclusive or missing. Sustained MRD negativity, which was evaluated in the intent-to-treat (ITT) population, was defined as the maintenance of MRD negativity in bone marrow confirmed ≥6 or ≥12 months apart.

Statistical Analyses

Methods supporting sample size determination and protocol-specified statistical analyses have been previously described.[10,23] Post hoc analyses of PFS by MRD status and/or response category were evaluated and a 2-sided *P* value was presented. PFS was compared between groups based on a log-rank test, and hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with a Cox regression model. Time-varying analyses were used to evaluate the correlation between PFS and response with MRD status. A univariate model was tested with

≥CR plus MRD negativity at multiple time points as the sole time-varying explanatory variable. All patients were considered MRD positive at baseline. A multivariate model with the following factors as covariates was also performed to determine whether the correlation was affected by any of these baseline factors: age (as reported in the case report form), ISS disease stage (I, II, III), baseline renal function (>60 mL/min, ≤60 mL/min), and cytogenetic risk (high, standard; risk was determined by fluorescence in situ hybridization or karyotype testing with high risk denoted by a positive test for any of the del17p, t(14;16), or t(4;14) molecular abnormalities). If values in baseline renal function or cytogenetic risk were missing, those patients were excluded from the multivariate model.

Data Sharing Statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu

Results

Patients

In total, 737 patients in MAIA (D-Rd, n = 368; Rd, n = 369) and 706 patients in ALCYONE (D-VMP, n = 350; VMP, n = 356) were randomized to the daratumumab and control groups (**Supplemental Figure 1**). Baseline characteristics were previously published.[10,23] The median

duration of follow-up was 36.4 (range, 0.0-49.9) months in MAIA and 40.1 (range, 0.0-52.1) months in ALCYONE.

MRD Negativity and Durability

In both MAIA and ALCYONE, daratumumab-based therapy led to improved rates of MRD negativity compared with the standard of care in both the ITT populations (D-Rd, 28.8% vs Rd, 9.2%; *P* <0.0001; D-VMP, 28.3% vs VMP, 7.0%; *P* <0.0001) and among patients who achieved ≥CR (D-Rd, 58.2% vs Rd, 34.0%; *P* = 0.0001; D-VMP, 58.8% vs VMP, 27.8%; *P* <0.0001; **Table 1**).

MRD durability was assessed among patients achieving ≥2 MRD-negative results lasting ≥6 or ≥12 months with no MRD positive result in between. In each study, daratumumab was associated with higher rates of sustained MRD negativity in the ITT population lasting ≥6 months (MAIA: D-Rd, 14.9% vs Rd, 4.3%; *P* <0.0001; ALCYONE: D-VMP, 15.7% vs VMP, 4.5%; *P* <0.0001) and ≥12 months (D-Rd, 10.9% vs Rd, 2.4%; *P* <0.0001; D-VMP, 14.0% vs VMP, 2.8%; *P* <0.0001; **Table 1**). Similar observations occurred among patients who achieved ≥CR; daratumumab-based therapies were associated with improved MRD durability lasting ≥6 months (MAIA: D-Rd, 30.2% vs 16.0%; *P* = 0.0097; ALCYONE: D-VMP, 34.4% vs VMP, 17.8%; *P* = 0.0055) and ≥12 months (D-Rd, 22.0% vs Rd, 9.0%; *P* = 0.0053; D-VMP, 30.6% vs VMP, 11.1%; *P* = 0.0006; **Table 1**).

Baseline demographic and disease characteristics by MRD durability (MRD negativity lasting ≥6 months, not lasting ≥6 months, ≥12 months or not lasting ≥12 months) among patients in MAIA and ALCYONE are summarized in **Supplemental Tables 1** and **2**. In general, baseline characteristics were comparable among patients who achieved sustained MRD negativity ≥12 months versus those who did not achieve ≥12 months MRD negativity within each study. Most characteristics reflected a comparable percentage of patients between treatment arms, but it should be noted that few patients (≤10) in the control arm of each study achieved sustained MRD negativity lasting ≥12 months. Among the small number of patients in the control arms who did achieve sustained MRD negativity ≥12 months, the majority were categorized as ISS stage I or II and had standard cytogenetic risk. In MAIA and ALCYONE, the proportion of patients with standard versus high cytogenetic risk was generally similar for those who achieved sustained MRD negativity compared with the ITT population (**Supplemental Tables 1** and **2**), although the number of patients in the high cytogenetic risk subgroups was small.

PFS and MRD Negativity

In the ITT populations of MAIA and ALCYONE, MRD-negative patients had improved PFS compared with MRD-positive patients (MAIA: HR, 0.15 [95% CI, 0.09-0.26]; *P* <0.0001; ALCYONE: HR, 0.23 [95% CI, 0.16-0.32]; *P* <0.0001; **Figure 1** and **Supplemental Figure 2**). Consistent with these findings, PFS was also improved for patients who achieved sustained MRD negativity lasting ≥6 months (**Figure 2**) or ≥12 months (**Figure 3**); similar analyses by treatment group demonstrated that the association of improved PFS with sustained MRD negativity was maintained regardless of treatment arm (**Supplemental Figures 3** and **4**). Furthermore, a combined analysis of patients from MAIA and ALCYONE who received

daratumumab-containing regimens (D-Rd and D-VMP, n = 718) or standard of care (Rd and VMP, n = 725) also demonstrated the clinical benefit of MRD negativity. PFS was prolonged in patients with sustained MRD durability lasting ≥6 months (**Supplemental Figure 5A**) or ≥12 months (**Supplemental Figure 5B**) compared with patients who did not achieve sustained MRD negativity or patients who were MRD positive.

In MAIA and ALCYONE, the median time to subsequent anticancer therapy (TTSAT) was not reached among daratumumab-treated patients who achieved MRD negativity or among patients who achieved MRD negativity in the control arm of MAIA. Among patients who were MRD positive, daratumumab therapy was associated with longer median TTSAT (MAIA: D-Rd, not reached vs Rd, 34.8 months; HR, 0.58 [95% CI, 0.44-0.75]; *P* <0.0001; ALCYONE: D-VMP, 43.8 months vs VMP, 24.9 months; HR, 0.53 [95% CI, 0.42-0.67]; *P* <0.0001; **Table 2**). For patients who were MRD negative at any time before initiating subsequent anticancer therapy, the risk of disease progression or death on the next subsequent line of therapy (PFS2) was not different for patients who received daratumumab-containing regimens or standard of care (**Table 2**); however, it should be noted that there were relatively few PFS2 events. Among patients who were MRD positive before subsequent anticancer therapy, PFS2 was not different for D-Rd versus Rd therapy; however, PFS2 was improved for patients who received D-VMP versus VMP (HR, 0.63 [95% CI, 0.48-0.82]; *P* = 0.0006; **Table 2**).

Although some variation occurred by treatment group, in general, estimated 36-month TTSAT rates were highest for patients with sustained MRD negativity lasting ≥6 months (MAIA: D-Rd,

96.1%, vs Rd, 100.0%; ALCYONE: D-VMP, 96.3% vs VMP, 93.8%; **Table 2**) and ≥12 months (MAIA: 94.6% vs 100.0%; ALCYONE: 95.8% vs 100.0%; **Table 2**) compared with patients who did not have MRD negativity lasting ≥6 months (MAIA: 98.0% vs 78.7%; ALCYONE: 72.7% vs 38.9%) and ≥12 months (MAIA: 98.5% vs 85.2%; ALCYONE: 76.2% vs 57.8%). Patients who were MRD positive had the shortest median time to next therapy (**Table 2**). In addition, estimated 24- and 36-month PFS2 rates were higher for MRD-negative patients compared with MRD-positive patients (**Table 2**).

PFS and MRD Negativity by Response Status

In a combined analysis of patients from MAIA and ALCYONE, based on patients who achieved ≥CR and MRD negativity (n = 259) compared with patients who had a response less than CR (very good partial response or less; ≤VGPR) or who were MRD positive (n = 1184), patients with the deepest response (≥CR and MRD negative) had improved PFS compared with patients who achieved ≤VGPR or who were MRD positive (HR, 0.19 [95% CI, 0.14-0.26]; *P* <0.0001; **Figure 4A**). This trend was maintained irrespective of therapy regimen (**Figure 4B**). Among patients achieving ≥CR with MRD negativity, daratumumab-containing regimens improved PFS compared with standard of care (HR, 0.51 [95% CI, 0.28-0.92]; *P* <0.0253; **Figure 4B**). In support of the observation that patients in the deepest response level had improved PFS, a time-varying model showed that ≥CR with MRD negativity had an effect on PFS in both univariate and multivariate analyses (**Supplemental Table 3**).

Discussion

This analysis from two phase 3 studies of daratumumab plus standard of care regimens for the treatment of transplant-ineligible NDMM provides evidence that MRD negativity is associated longer PFS, and that this benefit is improved for patients who reach durable MRD negativity lasting ≥6 or ≥12 months. While MRD negativity and durability were associated with improved PFS regardless of treatment regimen, daratumumab-based therapies drove more patients to achieve MRD-negative status and maintain MRD negativity for ≥6 and ≥12 months. It is possible that daratumumab-based therapies may induce longer periods of MRD negativity and deeper response; however, it is also possible that the continuous exposure to daratumumab alone or in combination with lenalidomide may have contributed to the longer periods of MRD negativity and deeper responses.

Our results are consistent with previous publications showing that MRD negativity is associated with improved PFS and OS for multiple myeloma,[1-11] including results from 2 meta-analyses of patients primarily with NDMM.[6,9] One analysis included 14 clinical studies and found MRD negativity to be correlated with improved PFS (HR, 0.41 [95% CI, 0.36-0.48]; *P* <0.001) and OS (HR, 0.57 [95% CI, 0.46-0.71]; *P* <0.001).[6] Another meta-analysis evaluated 6 NDMM studies, including data from the primary analysis of ALCYONE, which are reported here; in that analysis, a correlation between MRD negativity and PFS was demonstrated by a weighted regression analysis.[9] These studies, however, were based on different MRD assessment methodologies, sensitivity thresholds, and collectively include diverse patient populations. In our study, we explore the correlation of MRD negativity with long-term outcomes including PFS and

PFS2 using consistent assessment techniques, sensitivity thresholds, and similar patient populations. At the clinical cut-off date for these analyses, OS data were immature for MAIA, limiting the analysis of MRD status and durability as a surrogate endpoint for survival.

The current analysis demonstrated that patients who were MRD negative versus MRD positive had longer times to subsequent anticancer therapy and improved PFS2. Moreover, patients with sustained MRD negativity lasting either ≥6 or ≥12 months had the longest time to subsequent therapy. While these data support the association of MRD negativity and durability with improved long-term outcomes, the impact on PFS2 requires longer follow-up due to the small number of events. Additionally, in ALCYONE, daratumumab therapy was associated with longer time to subsequent anticancer therapy not only for MRD-negative patients but also among MRD-positive patients, and daratumumab led to improved PFS2 among MRD-positive patients. Interestingly, this observation demonstrates a clinical benefit of daratumumab even among patients who do not reach MRD negativity.

A strength of this study is its focus on patients with transplant-ineligible NDMM with similar baseline demographic and disease characteristics who were prospectively enrolled in one of two phase 3 clinical studies. These patients benefitted from undergoing consistent MRD assessment methodologies at the same sensitivity threshold, underscoring the robustness of the dataset. Moreover, we also present strong evidence from a pooled analysis of patients from MAIA and ALCYONE, showing that patients who achieved deep response (≥CR and MRD negative) had improved PFS compared with patients who were MRD positive or had a response less than CR

(≤VGPR). These data are supported by other studies that demonstrate PFS and OS were prolonged in MRD-negative patients with NDMM,[1-3,5,7,8] and in a previous report that achievement of CR in the absence of MRD negativity was not associated with prolonged PFS or OS.[5] Taken together with data from the current study, this evidence suggests that focusing only on hematologic response (CR) without consideration of MRD status limits the prognostic impact for clinical outcomes.

These data together with observations from the current analysis indicate durable MRD negativity lasting ≥6 or ≥12 months may represent yet a deeper level of response with a higher prognostic value, suggesting MRD negativity may be a more robust evaluation of disease control if sustained over time. The present study supports this view by demonstrating improved PFS with sustained MRD negativity.

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Authorship

Contribution: JS-M, HA-L, BP, SK, MAD, TF, M-VM, CT, AJ, SZU, GC, MC, and HQ contributed to study design, data acquisition, and contributed to data analysis or interpretation; JU, PR, HP, Mia Qi, SS, JW, MK, ND, CH, RVR, AK, RK, and Ming Qi contributed to study design and contributed to data analysis or interpretation; and all authors reviewed the manuscript, approved the final version, decided to publish this report, and vouch for data accuracy and completeness.

Disclosure of Conflicts of Interest

JS-M served as a consultant and on an advisory board for, Amgen, Bristol Myers Squibb, Celgene, Janssen, MSD, Novartis, Takeda, Roche, Sanofi, and GSK, AbbVie, and Karyopharm. HA-L received honoraria from and served on a speakers bureau for Celgene, Amgen, Bristol Myers Squibb, Sanofi, and Janssen; and received research funding from Celgene and Janssen. BP served as a consultant for and received honoraria from Amgen, Bristol Myers Squibb Celgene, Janssen, and Takeda; and received research support from Bristol Myers Squibb Celgene, Sanofi, and Roche. SK received research funding from and served as a consultant and on an advisory board for Celgene, Takeda, Janssen, AbbVie, Adaptive, KITE, and Medimmune/Astra Zeneca; received research funding from Merck, Novartis, Roche, and Sanofi; and was an IRC member for Oncopeptides. MAD received honoraria from Amgen, Takeda, Bristol Myers Squibb, Janssen, Celgene, and Beigene. TF served on a speaker's bureau for Janssen, Bristol Myers Squibb, and Takeda; and served on advisory boards for Janssen, Bristol Myers Squibb, Takeda, Roche, Amgen, Karyopharm, Sanofi, and Oncopeptides. M-VM received honoraria from and

served on an advisory board for Janssen, Celgene, Amgen, Takeda, AbbVie, GSK, Adaptive, Roche, Genentech, Pfizer, and Regeneron. CT has no conflicts to disclose. AJ received honoraria from and served as a consultant or on an advisory board for AbbVie, Amgen, Celgene/Bristol Myers Squibb, GSK, Janssen, and Karyopharm. SZU received research support personal fees from Amgen, Celgene, Sanofi, Seattle Genetics, Janssen, Takeda, SkylineDX, and Merck; received personal fees from AbbVie and MundiPharma; and received research support from Bristol Myers Squibb and Pharmacyclics. GC received honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen, Takeda, Roche and Sanofi; and received research support from Celgene, Janssen, and Takeda. MC received honoraria from and served on a speakers bureau for Janssen, Celgene Bristol Myers Squibb, Sanofi, Takeda, Amgen, MundiPharma, AbbVie, Adaptive, and GSK; and served on a speakers bureau for Janssen and Celgene Bristol Myers Squibb. HQ received research funding from Amgen, Sanofi, Celgene, Karyopharm, and GSK; and served on steering committees or advisory boards for Amgen, Celgene, Karyopharm, GSK, Janssen Cilag, and Sanofi. JU was an employee of Janssen at the time of study and my hold stock. PR, HP, Mia Qi, SS JW, MK, ND, CH, RVR, AK, RK, Ming Qi are employees of Janssen and may hold stock. NJB received honoraria from and served as a consultant for AbbVie, Amgen, GSK, Janssen, and Karyopharm; received research funding, honoraria, and served as a consultant for Celgene/Bristol Myers Squibb; and received honoraria from Takeda.

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Table 1. Rates of Sustained MRD-negativity Status in Transplant-ineligible NDMM

	MAIA			ALCYONE[a]		
MRD negativity (10^{-5})	**D-Rd**	**Rd**	***P* value[b]**	**D-VMP**	**VMP**	***P* value[b]**
Intention-to-treat	N = 368	N = 369		N = 350	N = 356	
MRD-negative status, n (%)	106 (28.8)	34 (9.2)	<0.0001	99 (28.3)	25 (7.0)	<0.0001
≥6 months sustained	55 (14.9)	16 (4.3)	<0.0001	55 (15.7)	16 (4.5)	<0.0001
≥12 months sustained	40 (10.9)	9 (2.4)	<0.0001	49 (14.0)	10 (2.8)	<0.0001
Complete response or better	N =182	N =100		N =160	N = 90	
MRD-negative status, n (%)	106 (58.2)	34 (34.0)	0.0001	94 (58.8)	25 (27.8)	<0.0001
≥6 months sustained	55 (30.2)	16 (16.0)	0.0097	55 (34.4)	16 (17.8)	0.0055
≥12 months sustained	40 (22.0)	9 (9.0)	0.0053	49 (30.6)	10 (11.1)	0.0006

MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide and dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

[a]MRD data from the intention-to-treat population of ALCYONE were reported previously.[11]

[b]*P* value was calculated using Fisher's exact test.

Table 2. Time to Next Therapy and Progression-Free Survival on Next Subsequent Line of Therapy

	MAIA		ALCYONE	
	D-Rd	**Rd**	**D-VMP**	**VMP**
	N = 368 (ITT)	**N = 369 (ITT)**	**N = 350 (ITT)**	**N = 356 (ITT)**
TTSAT by MRD status				
MRD negative (10^{-5}) at ≥1 time point, n (%)[a]	106 (28.8%)	34 (9.2%)	99 (28.3%)	25 (7.0%)
Number of events (%); number censored (%)[b]	5 (4.7%); 101 (95.3%)	2 (5.9%); 32 (94.1%)	16 (16.2%); 83 (83.8%)	9 (36.0%); 16 (64.0%)
Median (95% CI), months	NR (42.5-NE)	NR (NE-NE)	NR (46.4-NE)	44.4 (36.5-NE)
HR (95% CI), *P* value	0.54 (0.10-2.95); *P* = 0.4661[c]		0.45 (0.20-1.01); *P* = 0.0480[c]	
24-month TTSAT rate, % (95% CI)	98.1 (92.6-99.5)	100.0 (100.0-100.0)	91.7 (84.1-95.8)	92.0 (71.6-97.9)
36-month TTSAT rate, % (95% CI)	96.9 (90.6-99.0)	90.5 (64.4-97.8)	86.2 (77.4-91.8)	75.3 (53.0-88.1)
MRD positive, n (%)[a]	262 (71.2%)	335 (90.8%)	251 (71.7%)	331 (93.0%)
Number of events (%); number censored (%)[b]	82 (31.3%); 180 (68.7%)	152 (45.4%); 183 (54.6%)	107 (42.6%); 144 (57.4%)	203 (61.3%); 128 (38.7%)
Median (95% CI), months	NR (NE-NE)	34.8 (29.2-NE)	43.8 (35.3-NE)	24.9 (21.9-27.3)
HR (95% CI), *P* value	0.58 (0.44-0.75); *P* <0.0001[c]		0.53 (0.42-0.67); *P* <0.0001[c]	
24-month TTSAT rate, % (95% CI)	76.3 (70.4-81.2)	60.4 (54.6-65.7)	67.1 (60.5-72.9)	52.0 (46.1-57.6)
36-month TTSAT rate, % (95% CI)	65.4 (58.7-71.2)	48.7 (42.6-54.5)	55.2 (48.4-61.6)	33.2 (27.7-38.8)

Achieved and remained MRD negative (10^{-5}) for ≥6 months, n (%)[a]	55 (14.9%)	16 (4.3%)	55 (15.7%)	16 (4.5%)
Number of events (%); number censored (%)[b]	2 (3.6%); 53 (96.4%)	0 (0%); 16 (100.0%)	5 (9.1%); 50 (90.9%)	3 (18.8%); 13 (81.3%)
Median (95% CI), months	NR (NE-NE)	NR (NE-NE)	NR (46.4-NE)	NR (44.4-NE)
HR (95% CI), *P* value	NR (0-NE); *P* = 0.4674[c]		0.53 (0.13-2.22); *P* = 0.3746[c]	
24-month TTSAT rate, % (95% CI)	98.2 (87.8-99.7)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
36-month TTSAT rate, % (95% CI)	96.1 (85.2-99.0)	100.0 (100.0-100.0)	96.3 (85.9-99.1)	93.8 (63.2-99.1)
MRD negativity (10^{-5}) not lasting ≥6 months, n (%)	51 (13.9%)	18 (4.9%)	44 (12.6%)	9 (1.7%)
Number of events (%); number censored (%)[b]	3 (5.9%); 48 (94.1%)	2 (11.1%); 16 (88.9%)	11 (25.0%); 33 (75.0%)	6 (66.7%); 3 (33.3%)
Median (95% CI), months	NR (42.48-NE)	NR (34.66-NE)	NR (NE-NE)	32.6 (14.1-NE)
HR (95% CI), *P* value	0.30 (0.4-2.17); *P* = 0.2069[c]		0.35 (0.13-0.96); *P* = 0.328[c]	
24-month TTSAT rate, % (95% CI)	98.0 (86.6-99.7)	100.0 (100.0-100.0)	80.8 (65.2-89.9)	77.8 (36.5-93.9)
36-month TTSAT rate, % (95% CI)	98.0 (86.6-99.7)	78.7 (31.8-95.1)	72.7 (55.9-83.9)	38.9 (9.3-68.7)
Achieved and remained MRD negative (10^{-5}) for ≥12 months, n (%)[a]	40 (10.9%)	9 (2.4%)	49 (14.0%)	10 (2.8%)
Number of events (%); number censored (%)[b]	2 (5.0%); 38 (95.0%)	0 (0%); 9 (100.0%)	4 (8.2%); 45 (91.8%)	1 (10.0%); 9 (90.0%)
Median (95% CI), months	NR (NE-NE)	NR (NE-NE)	NR (46.4-NE)	NR (44.4-NE)

HR (95% CI), *P* value	NR (0-NE); *P* = 0.4975[c]		0.99 (0.11-8.86); *P* = 0.9897[c]	
24-month TTSAT rate, % (95% CI)	97.5 (83.5-99.6)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
36-month TTSAT rate, % (95% CI)	94.6 (80.1-98.6)	100.0 (100.0-100.0)	95.8 (84.2-98.9)	100.0 (100.0-100.0)
MRD negativity (10^{-5}) not lasting ≥12 months, n (%)	66 (17.9%)	25 (6.8%)	50 (14.3%)	15 (4.2%)
Number of events (%); number censored (%)[b]	3 (4.5%); 63 (95.5%)	2 (8.0%); 23 (92.0%)	12 (24.0%); 38 (76.0%)	8 (53.3%); 7 (46.7%)
Median (95% CI), months	NR (42.48-NE)	NR (34.66-NE)	NR (44.2-NE)	37.0 (27.6-NE)
HR (95% CI), *P* value	0.30 (0.04-2.17); *P* = 0.2082[c]		0.45 (0.18-1.10); *P* = 0.0724[c]	
24-month TTSAT rate, % (95% CI)	98.5 (89.6-99.8)	100.0 (100.0-100.0)	83.2 (69.2-91.2)	86.7 (56.4-96.5)
36-month TTSAT rate, % (95% CI)	98.5 (89.6-99.8)	85.2 (47.6-96.6)	76.2 (61.1-86.1)	57.8 (29.0-78.4)
PFS2[d]				
MRD negative (10^{-5}) at ≥1 time point, n (%)[a]	106 (28.8%)	34 (9.2%)	99 (28.3%)	25 (7.0%)
Number of events (%); number censored (%)[b]	6 (5.7%); 100 (94.3%)	4 (11.8%); 30 (88.2%)	18 (18.2%); 81 (81.8%)	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[c]		1.19 (0.40-3.51); *P* = 0.7551[c]	
24-month PFS2 rate, % (95% CI)	97.2 (91.5-99.1)	97.1 (80.9-99.6)	91.8 (84.4-95.8)	100.0 (100.0-100.0)
36-month PFS2 rate, % (95% CI)	95.0 (88.4-97.9)	83.9 (61.3-93.9)	84.6 (75.7-90.4)	92.0 (71.6-97.9)

MRD positive, n (%)[a]	262 (71.2%)	335 (90.8%)	251 (71.7%)	331 (93.0%)
Number of events (%); number censored (%)[b]	90 (34.4%); 172 (65.6%)	117 (34.9%); 218 (65.1%)	84 (33.5%); 167 (66.5%)	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[c]		0.63 (0.48-0.82); *P* = 0.0006[c]	
24-month PFS2 rate, % (95% CI)	76.4 (70.7-81.2)	75.5 (70.3-80.0)	78.7 (72.9-83.3)	73.5 (68.1-78.1)
36-month PFS2 rate, % (95% CI)	65.5 (59.0-71.3)	61.5 (55.3-67.0)	68.5 (62.2-74.1)	51.9 (45.9-57.6)

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

[a]Percentages calculated using the total number of patients in each column heading (ITT population) as the denominator.

[b] Percentages calculated using the number of patients in each column from the row immediately above number of events (%); number censored (%).

[c]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.

[d]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.

Figure Legends

Figure 1. PFS based on MRD status (10^{-5}) in MAIA (A), 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 MRD-negative patient populations and orange lines show MRD-positive patient populations (D-Rd/Rd shown for MAIA [A]; D-VMP/VMP for ALCYONE [B]; and D-Rd/Rd/D-VMP/VMP for all studies combined [C]). 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; HR, hazard ratio; CI, confidence interval.

Figure 2. PFS based on sustained MRD negativity (10^{-5}; ≥6 months) in MAIA (A), ALCYONE (B), and in both studies pooled (C). 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 (D-Rd/Rd shown for MAIA [A]; D-VMP/VMP for ALCYONE [B]; and D-Rd/Rd/D-VMP/VMP for all studies combined [C]). 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.

Figure 3. PFS based on sustained MRD negativity (10^{-5}; ≥12 months) in MAIA (A), ALCYONE (B), and in both studies pooled (C). 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 MRD-negative patient populations and orange lines show MRD-positive patient populations (D-Rd/Rd shown for MAIA [A]; D-VMP/VMP for ALCYONE [B]; and D-Rd/Rd/D-VMP/VMP for all studies combined [C]). 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.

Figure 4. PFS by response and MRD status (10^{-5}) among all patients in MAIA and ALCYONE (A), and in the pooled daratumumab-based combination groups versus control groups (B). Shown are Kaplan-Meier estimates of PFS based on MRD negativity and response category (≥CR, ≤VGPR) in the ITT populations. MRD negativity was assessed at a threshold of 1 tumor cell per 10^5 white blood cells. In panel A, purple line shows patients who achieved ≥CR and MRD negativity at any time since randomization; orange line shows patients who achieved ≤VGPR or who were MRD positive. In panel B, 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; CR, complete response; VGPR, very good partial response; ITT, intent to treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone;

Rd, lenalidomide/dexamethasone; VMP, bortezomib/melphalan/prednisone; HR, hazard ratio; CI, confidence interval; Dara, daratumumab.

Figure 1. PFS based on MRD status (10^{-5}) in MAIA (A), ALCYONE (B).

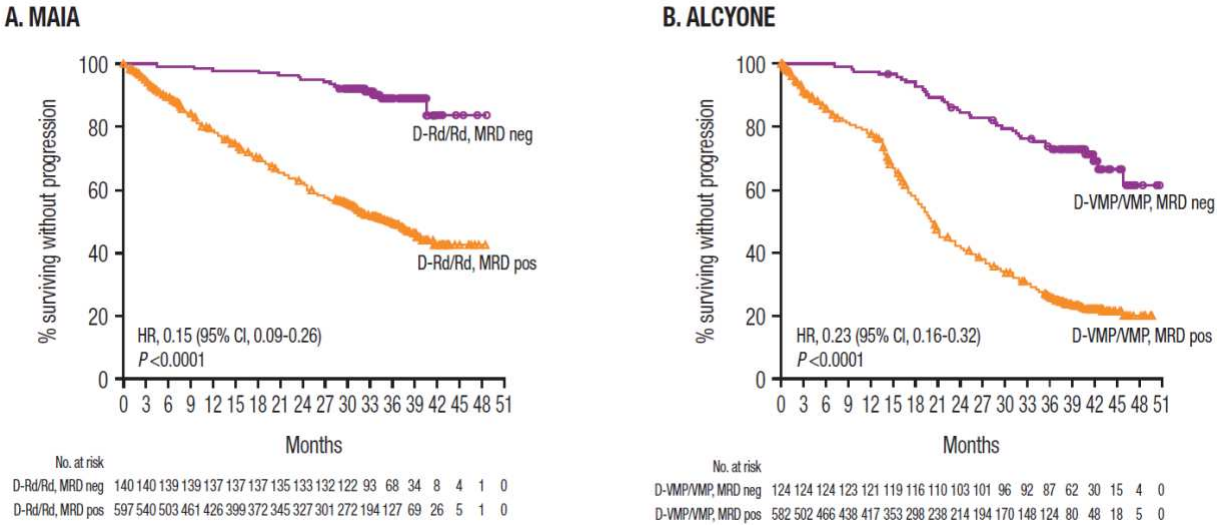


Figure 2. PFS based on sustained MRD negativity (10^{-5}; ≥6 months) in MAIA (A), ALCYONE (B), and in both studies pooled (C).

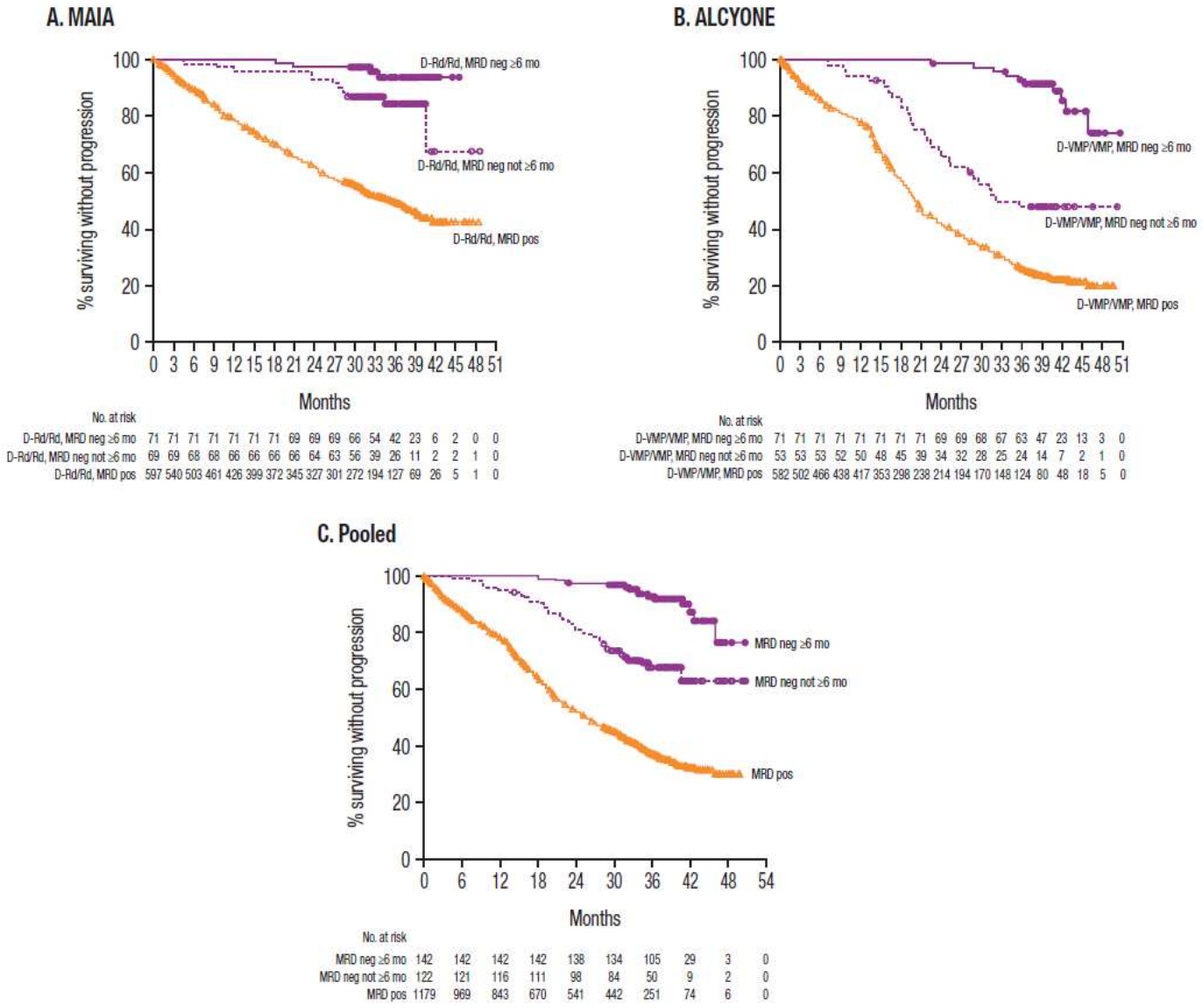


Figure 3. PFS based on sustained MRD negativity (10^{-5}; ≥12 months) in MAIA (A), ALCYONE (B), and in both studies pooled (C).

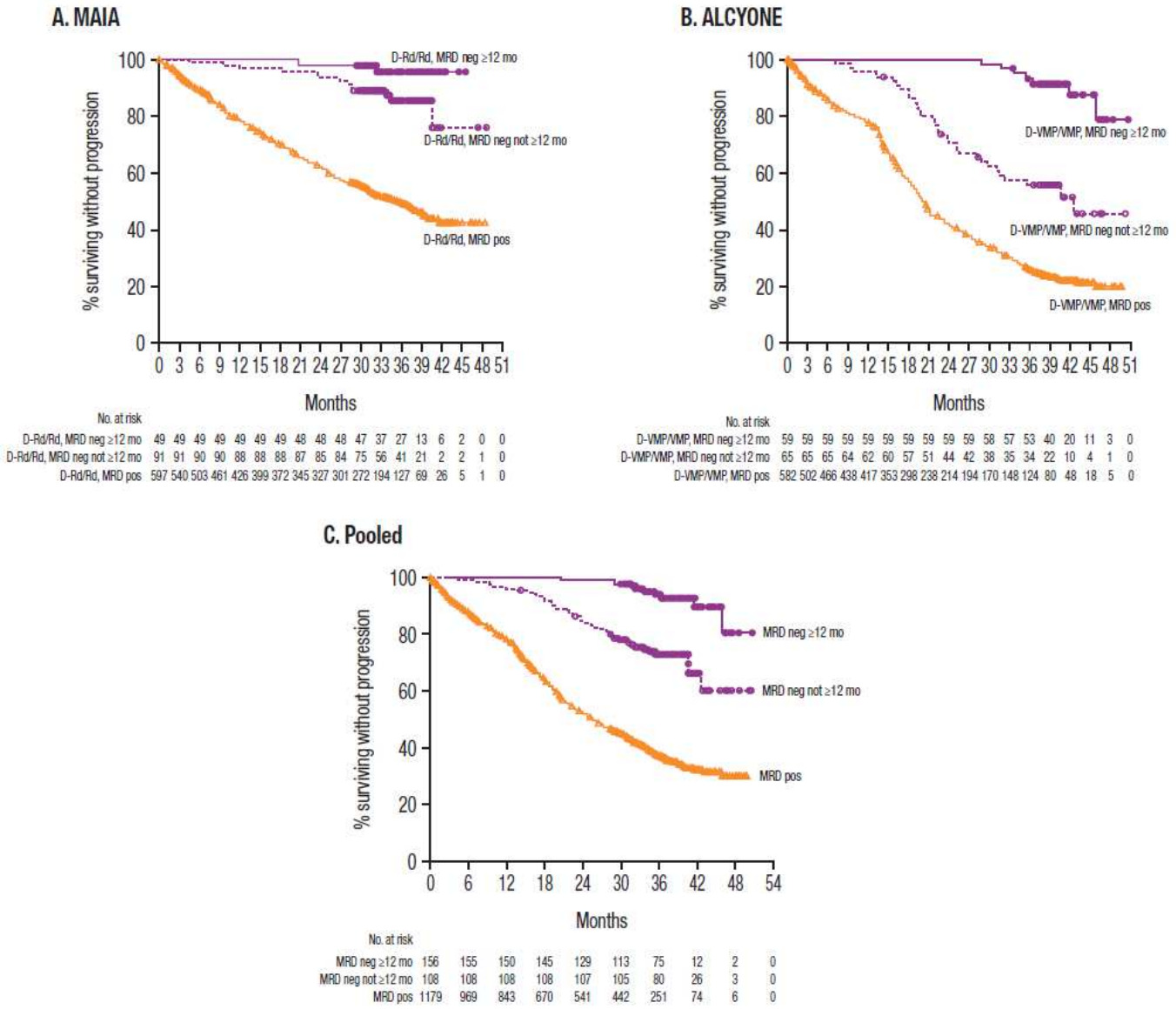
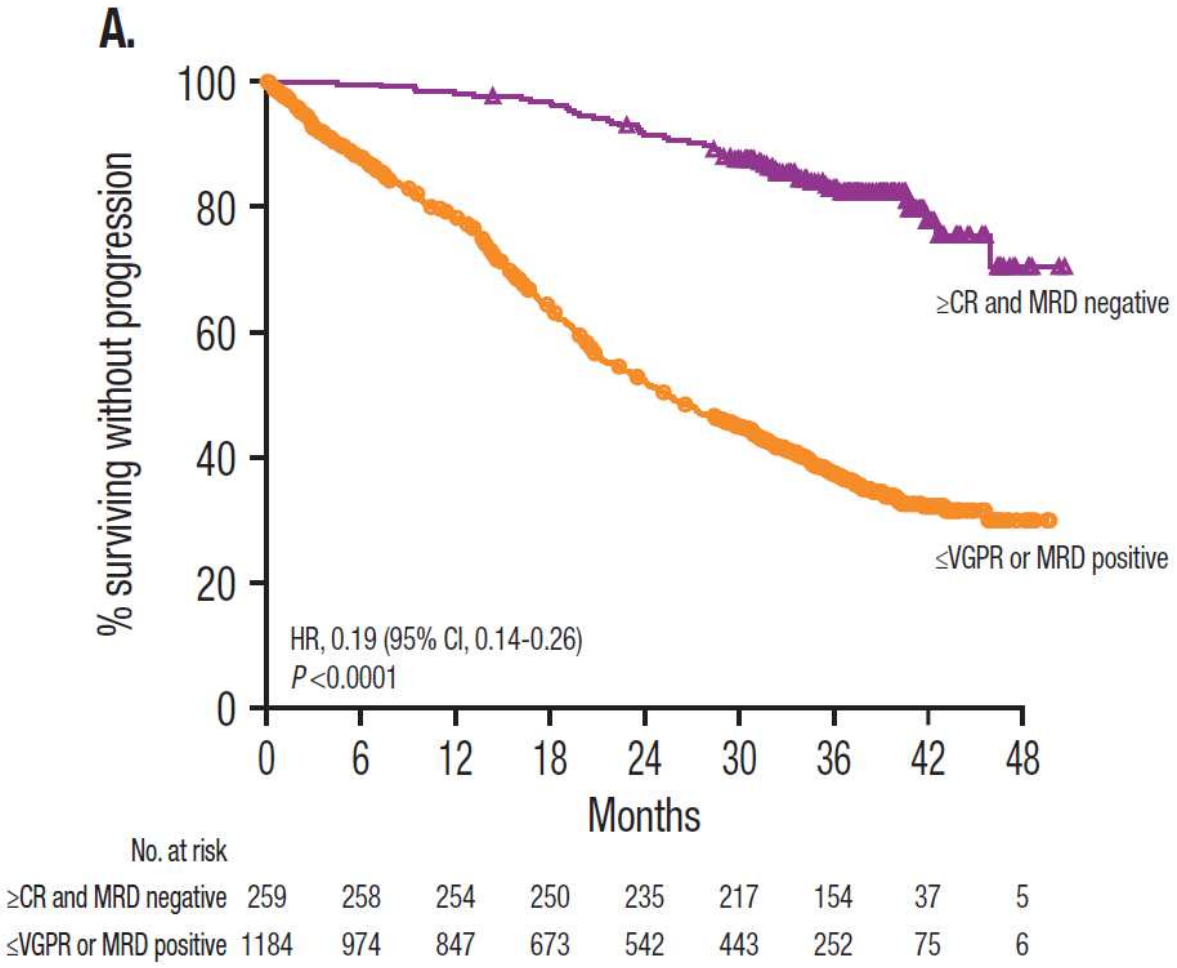
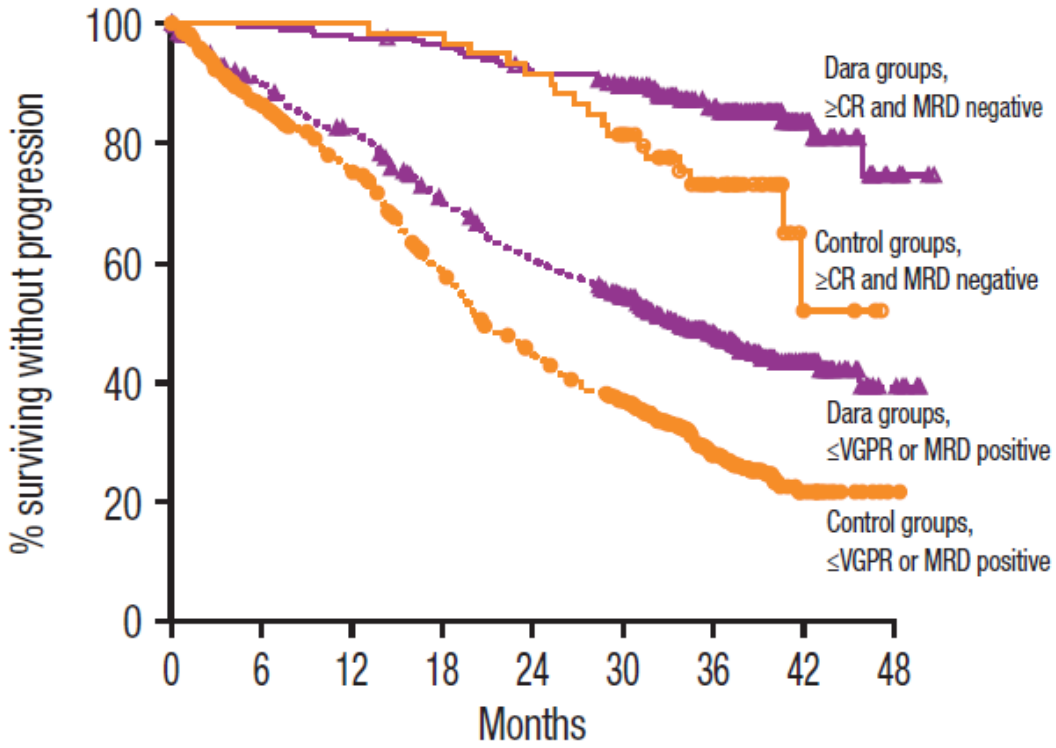


Figure 4. PFS by response and MRD status (10^{-5}) among all patients in MAIA and ALCYONE (A), and in the pooled daratumumab-based combination groups versus control groups (B).



B.



No. at risk									
Dara groups, ≥CR and MRD negative	200	199	195	192	181	171	128	34	5
Dara groups, ≤VGPR or MRD positive	518	448	406	341	292	250	163	53	5
Control groups, ≥CR and MRD negative	59	59	59	58	54	46	26	3	0
Control groups, ≤VGPR or MRD positive	666	526	441	332	250	193	89	22	1

Groups	HR (95% CI)	*P* value
Dara groups, ≥CR and MRD negative vs Control groups, ≥CR and MRD negative	0.51 (0.28-0.92)	0.0253
Dara groups, ≥CR and MRD negative vs Dara groups, ≤VGPR or MRD positive	0.21 (0.14-0.30)	<0.0001
Dara groups, ≥CR and MRD negative vs Control groups, ≤VGPR or MRD positive	0.12 (0.09-0.18)	<0.0001

Supplemental Material

Supplemental Table 1. 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)	≥6months (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, nn (%)												
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 2. 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 = 99)	≥6 months (n = 55)	Not ≥6 months (n = 44)	≥12 months (n = 49)	Not ≥12 months (n = 50)	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%)	72 (72.7%)	39 (70.9%)	33 (75.0%)	36 (73.5%)	36 (72.0%)	249 (69.9%)	15 (60.0%)	10 (62.5%)	5 (55.6%)	6 (60.0%)	9 (60.0%)
≥75 years	104 (29.7%)	27 (27.3%)	16 (29.1%)	11 (25.0%)	13 (26.5%)	14 (28.0%)	107 (30.1%)	10 (40.0%)	6 (37.5%)	4 (44.4%)	4 (40.0%)	6 (40.0%)
Sex, n (%)												
Male	160 (45.7%)	39 (39.4%)	17 (30.9%)	22 (50.0%)	14 (28.6%)	25 (50.0%)	167 (46.9%)	10 (40.0%)	5 (31.3%)	5 (55.6%)	4 (40.0%)	6 (40.0%)
Female	190 (54.3%)	60 (60.6%)	38 (69.1%)	22 (50.0%)	35 (71.4%)	25 (50.0%)	189 (53.1%)	15 (60.0%)	11 (68.8%)	4 (44.4%)	6 (60.0%)	9 (60.0%)
Race, n (%)												
White	297 (84.9%)	81 (81.8%)	47 (85.5%)	34 (77.3%)	41 (83.7%)	40 (80.0%)	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 (18.2%)	8 (14.5%)	10 (22.7%)	8 (16.3%)	10 (20.0%)	52 (14.6%)	2 (8.0%)	2 (12.5%)	0	2 (20.0%)	0
ECOG performance status, n (%)												
0	78 (22.3%)	17 (17.2%)	11 (20.0%)	6 (13.6%)	11 (22.4%)	6 (12.0%)	99 (27.8%)	7 (28.0%)	4 (25.0%)	3 (33.3%)	2 (20.0%)	5 (33.3%)
1	182 (52.0%)	55 (55.6%)	27 (49.1%)	28 (63.6%)	22 (44.9%)	33 (66.0%)	173 (48.6%)	10 (40.0%)	8 (50.0%)	2 (22.2%)	4 (40.0%)	6 (40.0%)
2	90 (25.7%)	27 (27.3%)	17 (30.9%)	10 (22.7%)	16 (32.7%)	11 (22.0%)	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%)	33 (33.3%)	19 (34.5%)	14 (31.8%)	18 (36.7%)	15 (30.0%)	140 (39.3%)	8 (32.0%)	4 (25.0%)	4 (44.4%)	4 (40.0%)	4 (26.7%)
IgA	49 (14.0%)	13 (13.1%)	7 (12.7%)	6 (13.6%)	6 (12.2%)	7 (14.0%)	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%)	17 (17.2%)	12 (21.8%)	5 (11.4%)	11 (22.4%)	6 (12.0%)	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 (7.1%)	3 (5.5%)	4 (9.1%)	2 (4.1%)	5 (10.0%)	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 (16.2%)	9 (16.4%)	7 (15.9%)	9 (18.4%)	7 (14.0%)	67 (18.8%)	5 (20.0%)	3 (18.8%)	2 (22.2%)	2 (20.0%)	3 (20.0%)
II	139 (39.7%)	42 (42.4%)	25 (45.5%)	17 (38.6%)	23 (46.9%)	19 (38.0%)	160 (44.9%)	10 (40.0%)	6 (37.5%)	4 (44.4%)	5 (50.0%)	5 (33.3%)
III	142 (40.6%)	41 (41.4%)	21 (38.2%)	20 (45.5%)	17 (34.7%)	24 (48.0%)	129 (36.2%)	10 (40.0%)	7 (43.8%)	3 (33.3%)	3 (30.0%)	7 (46.7%)
Cytogenetic profile[c]												
Patients evaluated	314	93	52	41	46	47	302	23	14	9	9	14

Standard-risk cytogenetic abnormality, n (%)	261 (83.1%)	76 (81.7%)	46 (88.5%)	30 (73.2%)	40 (87.0%)	36 (76.6%)	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%)	17 (18.3%)	6 (11.5%)	11 (26.8%)	6 (13.0%)	11 (23.4%)	45 (14.9%)	4 (17.4%)	3 (21.4%)	1 (11.1%)	2 (22.2%)	2 (14.3%)
del(17p)	29 (9.2%)	9 (9.7%)	4 (7.7%)	5 (12.2%)	4 (8.7%)	5 (10.6%)	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	0.76	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 3. Time-varying Survival Cox Proportional Hazard Model for PFS.

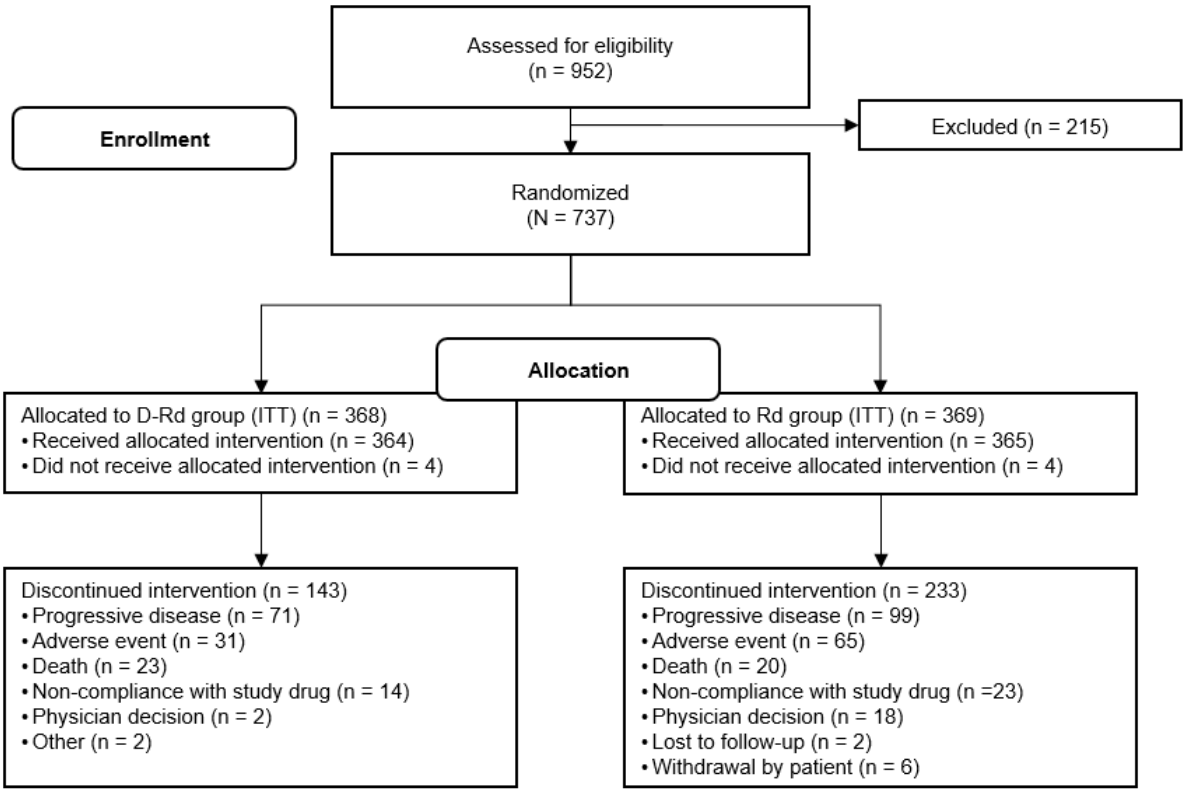
Variable	Hazard ratio (95% CI)	*P* value
Univariate analysis		
Response group (≥CR and MRD$^-$ vs ≤VGPR or MRD$^+$)	0.18 (0.11-0.28)	<0.0001
Multivariate analysis		
Response group (≥CR and MRD$^-$ vs ≤VGPR or MRD$^+$)	0.18 (0.11-0.29)	<0.0001
Age	1.00 (0.98-1.01)	0.533
ISS disease stage (II vs I)	1.77 (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; CI, confidence interval; CR, complete response; MRD, minimal residual disease; VGPR, very good partial response; ISS, International Staging System.

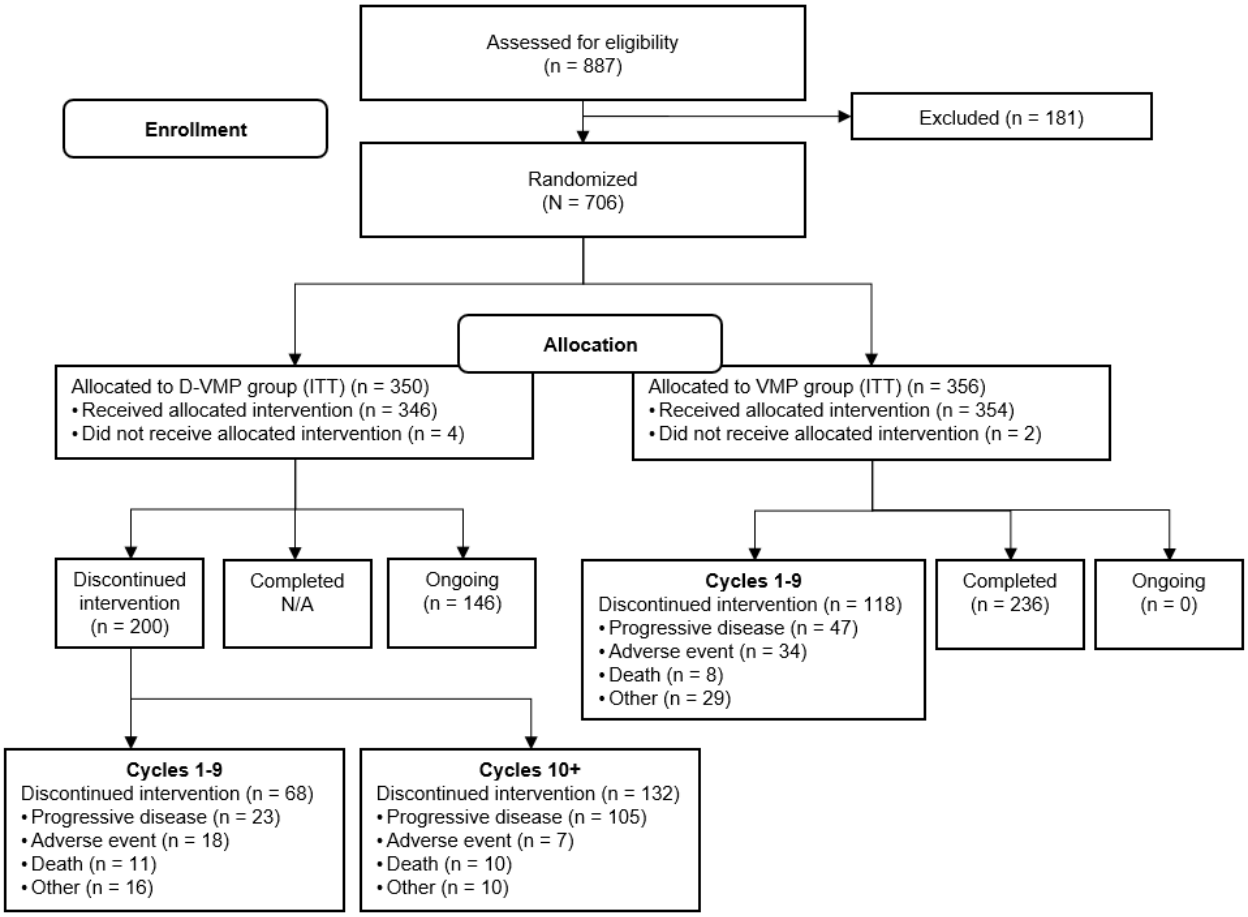
Data are for a univariate and multivariate analysis of combined data from the MAIA and ALCYONE studies evaluating the following variables: MRD-negativity status and response at each time point, age, ISS disease stage, baseline renal function, and cytogenetic risk. Patients with missing baseline renal function groups or cytogenetic risk groups 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.

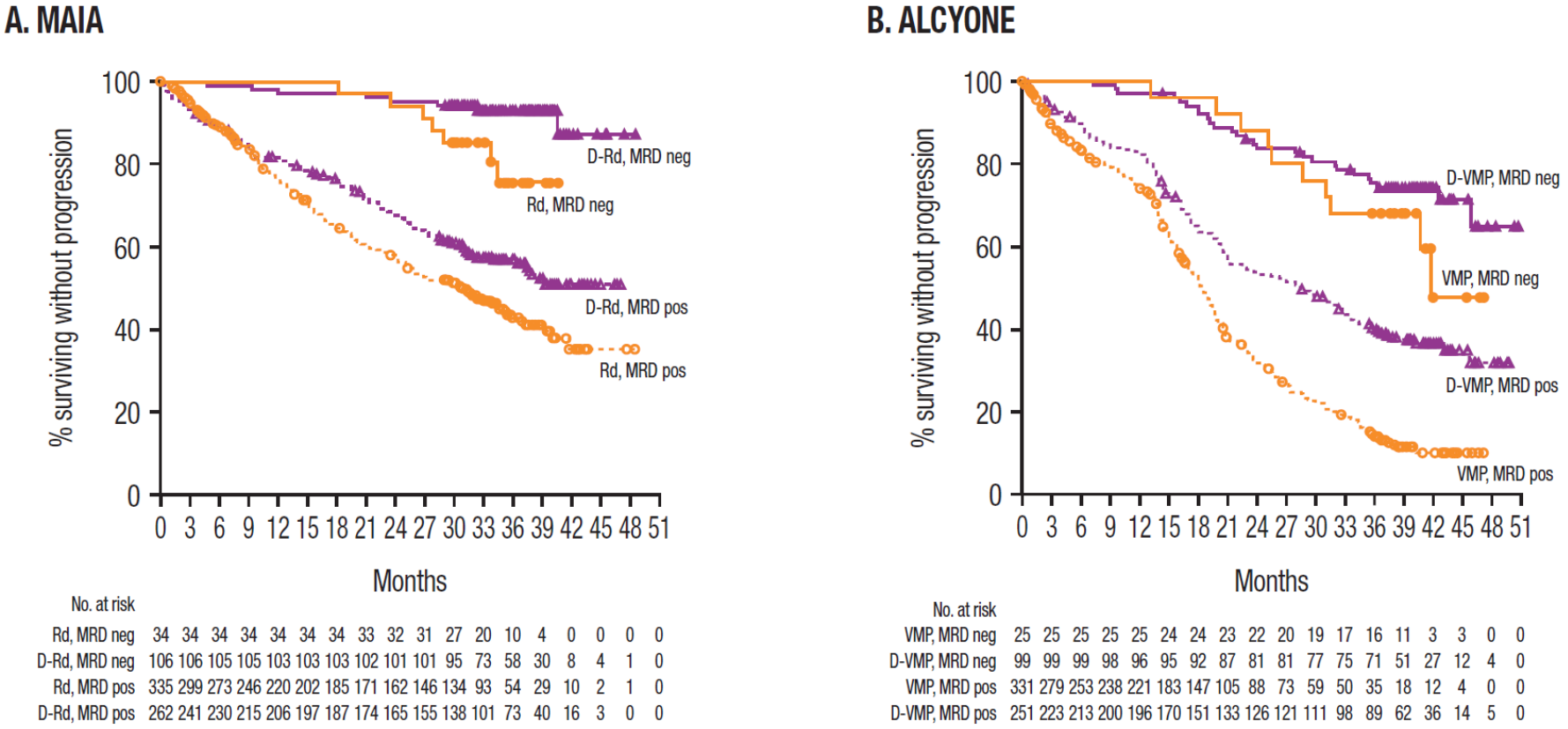
(A) MAIA



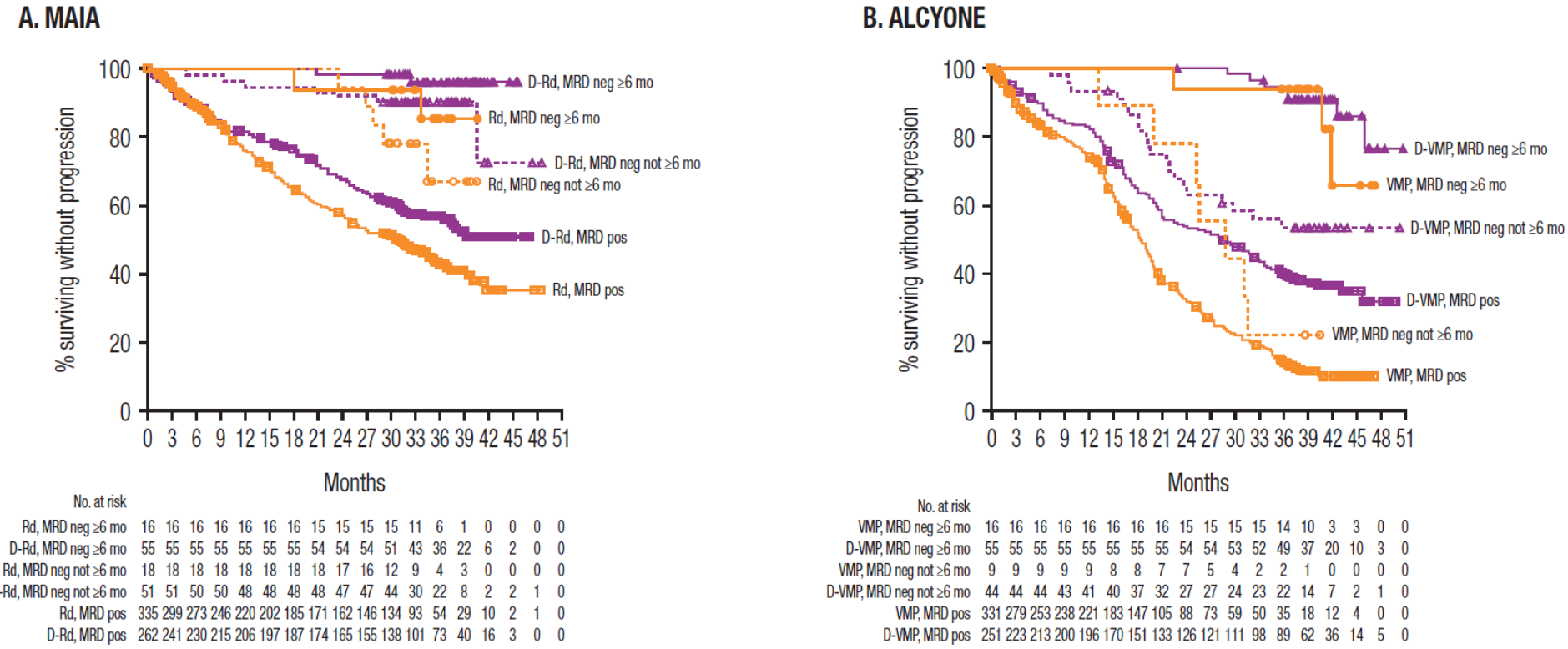
(B) ALCYONE[11]


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)

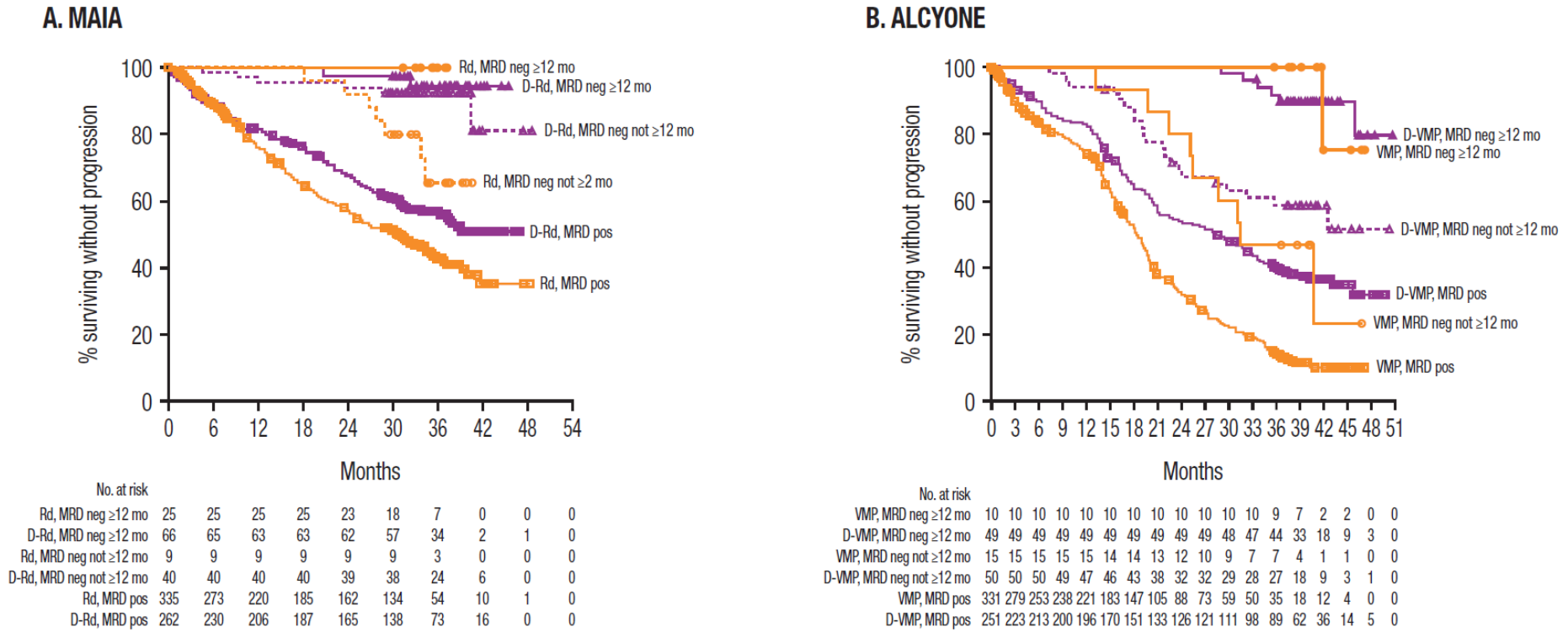
Supplemental Figure 2. PFS by treatment group based on MRD status (10^{-5}) in MAIA (A) and ALCYONE (B). Shown are Kaplan-Meier estimates of PFS by MRD status among patients in the ITT populations. MRD was assessed at a threshold of 1 tumor cell per 10^5 white blood cells. Purple lines show regimens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



Supplemental Figure 3. PFS by treatment group based on sustained minimal residual disease (MRD) negativity (10^{-5}; ≥6 months) in MAIA (A) and ALCYONE (B). 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 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 and dexamethasone; D-VMP, daratumumab plus bortezomib, melphalan, and prednisone; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

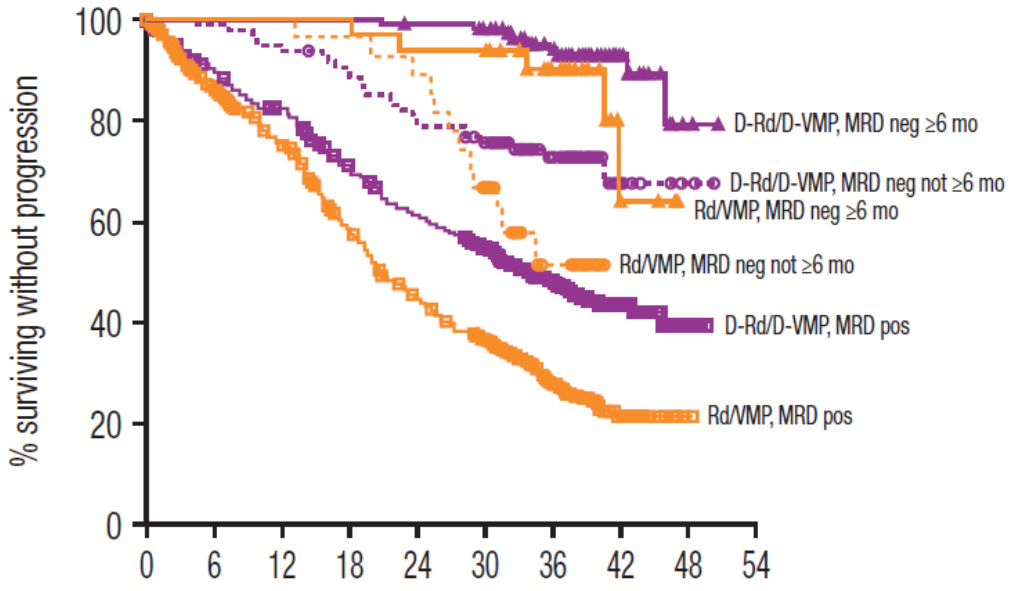


Supplemental Figure 4. PFS by treatment group based on sustained MRD negativity (10^{-5}; ≥12 months) in MAIA (A) and ALCYONE (B). Shown are Kaplan-Meier estimates of PFS by sustained MRD negativity lasting ≥12 months among patients in the ITT populations. MRD status was assessed at a threshold of 1 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 based on 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 and dexamethasone; D-VMP, daratumumab plus bortezomib, melphalan, and prednisone; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.



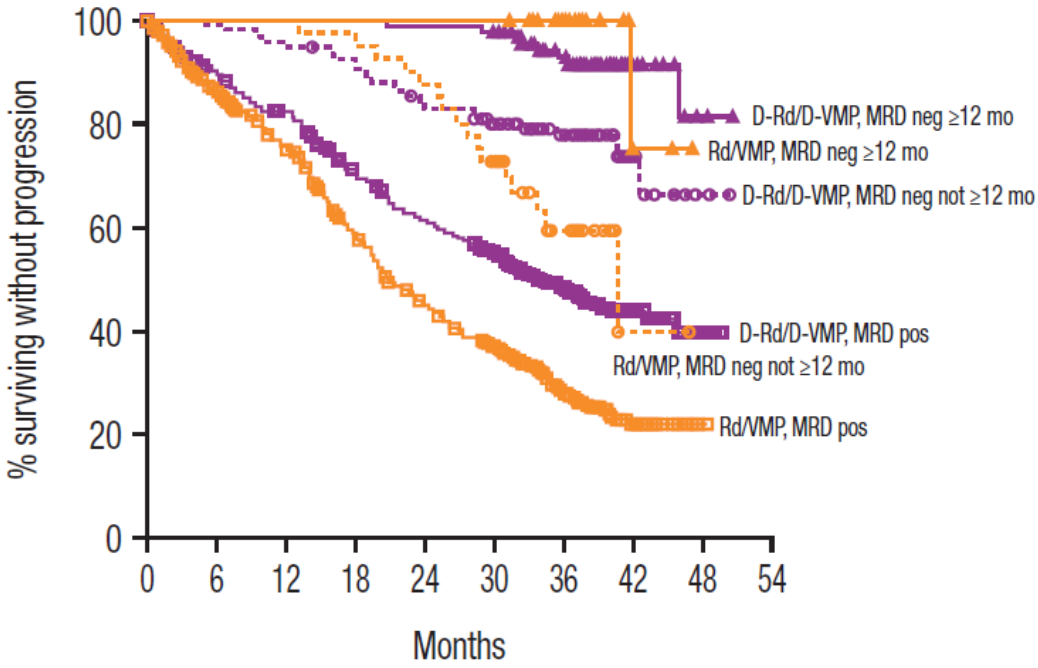
Supplemental Figure 5. PFS based on sustained MRD (10^{-5}) negativity lasting ≥6 months (A) or ≥12 months (B) in the pooled daratumumab-based combination groups (D-Rd/D-VMP) versus the pooled control groups (Rd/VMP) in MAIA and ALCYONE. Shown are the results of the Kaplan-Meier estimates of PFS among 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 and dexamethasone; D-VMP, daratumumab plus bortezomib, melphalan, and prednisone; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone; ITT, intent to treat.

A.



No. at risk										
Rd/VMP, MRD neg ≥6 mo	32	32	32	32	30	30	20	3	0	0
D-Rd/D-VMP, MRD neg ≥6 mo	110	110	110	110	108	104	85	26	3	0
Rd/VMP, MRD neg not ≥6 mo	27	27	27	26	24	16	6	0	0	0
D-Rd/D-VMP, MRD neg not ≥6 mo	95	94	89	85	74	68	44	9	2	0
Rd/VMP, MRD pos	666	526	441	332	250	193	89	22	1	0
D-Rd/D-VMP, MRD pos	513	443	402	338	291	249	162	52	5	0

B.



No. at risk

Rd/VMP, MRD neg ≥12 mo	19	19	19	19	19	19	12	2	0	0
D-Rd/D-VMP, MRD neg ≥12 mo	89	89	89	89	88	86	68	24	3	0
Rd/VMP, MRD neg not ≥12 mo	40	40	40	39	35	27	14	1	0	0
D-Rd/D-VMP, MRD neg not ≥12 mo	116	115	110	106	94	86	61	11	2	0
Rd/VMP, MRD pos	666	526	441	332	250	193	89	22	1	0
D-Rd/D-VMP, MRD pos	513	443	402	338	291	249	162	52	5	0