# Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR

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## Abstract

**CASTOR showed the significant clinical benefit of daratumumab plus bortezomib and dexamethasone for patients with previously treated multiple myeloma. With ~3 years median follow-up, this regimen continues to demonstrate significantly improved progression-free survival with higher minimal residual disease–negativity rates and consistent safety, with the greatest benefit observed when used earlier in the treatment of relapsed/refractory multiple myeloma.**

**Background:** In the phase III CASTOR study in relapsed or refractory multiple myeloma, daratumumab, bortezomib, and dexamethasone (D-Vd) demonstrated significant clinical benefit versus Vd alone. Outcomes after 40.0 months of median follow-up are discussed. **Patients and Methods:** Eligible patients had received ≥ 1 line of treatment and were administered bortezomib (1.3 mg/m$^2$) and dexamethasone (20 mg) for 8 cycles with or without daratumumab (16 mg/kg) until disease progression. **Results:** Of 498 patients in the intent-to-treat (ITT) population (D-Vd, n = 251; Vd, n = 247), 47% had 1 prior line of treatment (1PL; D-Vd, n = 122; Vd, n = 113). Median progression-free survival (PFS) was significantly prolonged with D-Vd versus Vd in the ITT population (16.7 vs. 7.1 months; hazard ratio [HR], 0.31; 95% confidence interval [CI], 0.25-0.40; $P < .0001$) and the 1PL subgroup (27.0 vs. 7.9 months; HR, 0.22; 95% CI, 0.15-0.32; $P < .0001$). In lenalidomide-refractory patients, the median PFS was 7.8 versus 4.9 months (HR, 0.44; 95% CI, 0.28-0.68; $P = .0002$) for D-Vd (n = 60) versus Vd (n = 81). Minimal residual disease (MRD)–negativity rates ($10^{-5}$) were greater with D-Vd versus Vd (ITT: 14% vs. 2%; 1PL: 20% vs. 3%; both $P < .0001$). PFS2 was significantly prolonged with D-Vd versus Vd (ITT: HR, 0.48; 95% CI, 0.38-0.61; 1PL: HR, 0.35; 95% CI, 0.24-0.51; $P < .0001$). No new safety concerns were observed. **Conclusion:** After 3 years, D-Vd maintained significant benefits in patients with relapsed or refractory multiple myeloma with a consistent safety profile. D-Vd provided the greatest benefit at first relapse and increased MRD-negativity rates.

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**Keywords:** Clinical trial, Efficacy, Minimal residual disease, Relapsed/refractory, Safety

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## Introduction

In recent years, considerable progress has been made in the treatment of multiple myeloma (MM) owing to the availability of novel agents for use in combination with standard-of-care treatment regimens.[1] However, responses to treatment are decreased in both duration and depth at each subsequent line of therapy, illustrating the need to incorporate the most effective therapies earlier in the treatment sequence to derive the greatest benefit from a given regimen.[2] The use of lenalidomide, an immunomodulatory agent (IMiD), is increasingly prevalent as initial treatment for newly diagnosed multiple myeloma (NDMM).[3] Many frontline treatment regimens are given until disease progression, thus limiting the value of retaining lenalidomide for the next line of treatment.[3] Proteasome inhibitor (PI)–based regimens are widely used for the treatment of MM but, in patients with relapsed or refractory multiple myeloma (RRMM), deep and sustained clinical responses are uncommon.[4-7] The addition of novel agents to PI-based therapy remains an active area of interest to address unmet needs for patients with RRMM.[3,5,8-10]

Daratumumab is a human, CD38-targeted, immunoglobulin (Ig) Gκ monoclonal antibody with a direct on-tumor and immunomodulatory mechanism of action.[11-16] In phase III studies in patients with NDMM and RRMM, daratumumab-based regimens reduced disease progression or death risk by ≥ 44%, doubled complete response (CR) rates, and tripled minimal residual disease (MRD)–negativity rates.[9,17-19] Based on these results, daratumumab has been approved in many countries both as a monotherapy for heavily pre-treated patients with RRMM,[20] and in combination with standard-of-care regimens for patients with RRMM[21] and patients with NDMM.[22,23]

The phase III CASTOR study enrolled patients with RRMM who had received at least 1 prior line of therapy.[24] In the most recent analysis of the study, the addition of daratumumab to the PI bortezomib and dexamethasone (D-Vd) significantly prolonged progression-free survival (PFS) and induced higher rates of deeper responses than bortezomib and dexamethasone (Vd) alone in patients with RRMM at a median follow-up of 19.4 months (median PFS, 16.7 vs. 7.1 months; hazard ratio [HR], 0.31; 95% confidence interval [CI], 0.24-0.39; $P < .0001$).[9] The PFS benefit of D-Vd was especially pronounced in a subgroup of patients who had received only 1 prior line of therapy (median PFS not reached for D-Vd compared with 7.9 months for Vd; HR, 0.19; 95% CI, 0.12-0.29; $P < .0001$).[9] Here, we provide updated efficacy and safety data for D-Vd versus Vd in CASTOR after a median follow-up of 40.0 months (nearly 3 years after the primary analysis).

## Patients and Methods

### *Study Design and Treatment*

The study design and patient population of CASTOR have been described previously.[9,24] Briefly, this phase III, multicenter, randomized, open-label, active-controlled trial enrolled patients with RRMM who had received at least 1 prior line of therapy. Patients were randomized 1:1 to receive D-Vd or Vd; randomization was stratified by International Staging System at baseline (I, II, or III), prior lines of therapy (1, 2, or > 3), and prior exposure to bortezomib (yes or no). All patients received eight 21-day cycles of 1.3 mg/m$^2$ subcutaneous bortezomib (days 1, 4, 8, and 11) and 20 mg oral dexamethasone (days 1, 2, 4, 5, 8, 9, 11, and 12). Patients in the D-Vd arm received 16 mg/kg intravenous daratumumab once weekly for cycles 1 through 3 and on day 1 of cycles 4 through 8. In the maintenance phase of the study (cycles 9+), patients in the D-Vd arm continued to receive daratumumab monotherapy once every 4 weeks until disease progression. After protocol amendment, patients receiving Vd were offered daratumumab monotherapy after disease progression.

### *Patients*

Patients were eligible if they had documented MM, had received at least 1 prior line of therapy (with at least a partial response [PR]), and had disease progression classified per International Myeloma Working Group criteria.[25] Patients were not eligible if they had disease refractory to bortezomib or another PI (prior bortezomib exposure was permitted). Cytogenetic risk was evaluated using local fluorescence in situ hybridization or karyotyping, assessed locally. High-risk patients had t(4;14), t(14;16), or del17p cytogenetic abnormalities.

### *Study Endpoints and Analyses*

Endpoints for this study included PFS (primary), time to disease progression, overall response rate (ORR), MRD negativity, and safety (secondary). Exploratory endpoints included subgroup analysis by number of lines and type of prior therapy, as described previously.[9] Efficacy analyses were based on the intent-to-treat (ITT) population unless otherwise specified. The response-evaluable subset included patients with measurable disease at screening or baseline who received ≥ 1 dose of study treatment and had ≥ 1 post-baseline disease assessment. The safety analysis set included all patients who received ≥ 1 dose of study treatment. PFS on the subsequent line of therapy (PFS2) was defined as the time from randomization to progressive disease after the next line of subsequent therapy or death.

The entire ITT population was evaluated to allow for a stringent and unbiased evaluation of MRD status. MRD was assessed at the time of suspected CR and at 6 and 12 months following the first treatment dose; an additional MRD evaluation was required every 12 months after CR. MRD was assessed via next-generation sequencing on bone marrow aspirate samples that were ficolled and evaluated by the United States Food and Drug Administration–approved clonoSEQ assay v2.0 (Adaptive Biotechnologies, Seattle, WA). Patients were considered to be MRD-positive if they had an MRD-positive test result or had no MRD assessment. The rate of MRD negativity was defined as the proportion of patients who achieved MRD-negative status (assessed at a sensitivity threshold of $10^{-5}$ [1 cancer cell per 100,000 nucleated cells]) at any time point following the first treatment dose, and compared using the Fisher exact test.

### *Study Oversight*

The study was registered at ClinicalTrials.gov (identification number: NCT02136134) and was sponsored by Janssen Research & Development, LLC. All clinical study sites' institutional review boards or ethics committees approved this study, with all patients

providing written informed consent. The study design and analyses were devised by the investigators and sponsor. The investigators and their research teams collected the study data. Janssen conducted the final data analysis and verified the accuracy of the data. The investigators were not restricted by confidentiality agreements and had full accessibility to all the data. Writing assistance was funded by Janssen Global Services, LLC.

## Results

### *Patients*

At the time of clinical cutoff for the presented analysis (October 2, 2018), 498 patients had received treatment. The demographics and baseline characteristics were well-balanced between treatment arms and have been described previously.[9,24] Briefly, the median age of patients was 64 years (range, 30-88 years), and patients had received a median of 2 prior lines of therapy (range, 1-9) (Table 1). The most frequent prior therapies were bortezomib (66%) and thalidomide (49%), and 48% of patients had received both a PI and an IMiD; 42% of patients had received prior lenalidomide. Lenalidomide-refractory patients had received a median of 2 prior lines of therapy (range, 1-10). A total of 122 (49%) patients in the D-Vd arm and 113 (46%) patients in the Vd arm had received a single line of treatment, most frequently including an alkylating agent (89%), IMiD (65%), or a PI (53%) (Table 1). Of these 235 patients with 1 prior line of treatment, 18% were refractory to that therapy; 10% of these patients were refractory to lenalidomide (6 patients receiving D-Vd and 18 patients receiving Vd). Demographics and baseline characteristics of patients with 1 prior line of treatment were consistent with the overall study population (Table 1).

### *Disposition and Drug Exposure*

At the time of this analysis, all patients in both treatment arms had completed the protocol-specified 8 cycles of treatment with bortezomib and dexamethasone or had discontinued study treatment. The median duration of treatment was 13.4 months (range, 0-46.6 months) for the 243 D-Vd–treated patients and 5.2 months (range, 0.2-8.0 months) for the 237 Vd-treated patients. Patients had received a median of 23 daratumumab infusions (range, 1-58). Overall, 297 (62%) patients had discontinued treatment, the majority (213 [44%] patients) owing to progressive disease. For the 191 D-Vd patients who received single-agent daratumumab maintenance therapy during cycles 9+, median (range) duration of monotherapy treatment was 14.8 months (range, 0.03-41.0 months), and 50 patients continue to receive treatment. A total of 81 patients in the Vd arm subsequently received single-agent daratumumab after disease progression; of these, 40 patients received single-agent daratumumab as the first subsequent line of therapy after disease progression on Vd.

**Table 1** Baseline Demographics and Clinical Characteristics

| Characteristic | ITT Population | | 1 Prior Line of Therapy Subgroup | |
|---|---|---|---|---|
| | D-Vd (n = 251) | Vd (n = 247) | D-Vd (n = 122) | Vd (n = 113) |
| **Age, y** | | | | |
| Median (range) | 64 (30-88) | 64 (33-85) | 63 (30-84) | 64 (40-85) |
| ≥75 | 23 (9) | 35 (14) | 8 (7) | 17 (15) |
| **ISS staging, n (%)**[a] | | | | |
| I | 98 (39) | 96 (39) | 57 (47) | 51 (45) |
| II | 94 (38) | 100 (41) | 42 (34) | 44 (39) |
| III | 59 (24) | 51 (21) | 23 (19) | 18 (16) |
| **Time from diagnosis, y** | | | | |
| Median (range) | 3.87 (0.7-20.7) | 3.72 (0.6-18.6) | 2.81 (0.7-14.9) | 2.98 (0.6-18.1) |
| **Prior lines of therapy, n (%)** | | | | |
| Median (range) | 2 (1-9) | 2 (1-10) | 1 (1-1) | 1 (1-1) |
| 1 | 122 (49) | 113 (46) | 122 (100) | 113 (100) |
| 2 | 70 (28) | 74 (30) | 0 | 0 |
| 3 | 37 (15) | 32 (13) | 0 | 0 |
| >3 | 22 (9) | 28 (11) | 0 | 0 |
| Prior PI, n (%) | 169 (67) | 172 (70) | 65 (53) | 59 (52) |
| Prior bortezomib | 162 (65) | 164 (66) | 62 (51) | 57 (50) |
| Prior IMiD, n (%) | 179 (71) | 198 (80) | 72 (59) | 81 (72) |
| Prior thalidomide | 125 (50) | 121 (49) | 58 (48) | 48 (43) |
| Prior lenalidomide | 89 (36) | 120 (49) | 15 (12) | 33 (29) |
| Prior PI + IMiD, n (%) | 112 (45) | 129 (52) | 29 (24) | 33 (29) |
| Refractory to lenalidomide, n (%) | 60 (24) | 81 (33) | 6 (5) | 18 (16) |

Abbreviations: D-Vd = daratumumab/bortezomib/dexamethasone; IMiD = immunomodulatory drug; ISS = International Staging System; ITT = intent-to-treat; PI = proteasome inhibitor; Vd = bortezomib/dexamethasone.
[a]ISS staging was based on the combination of serum β2-microglobulin and albumin.

### *Efficacy*

After a median follow-up of 40.0 months, PFS was significantly prolonged for patients receiving D-Vd versus Vd in the ITT population (median PFS, 16.7 months D-Vd vs. 7.1 months Vd; HR, 0.31; 95% CI, 0.25-0.40; $P < .0001$) (Figure 1A). This PFS benefit was maintained across patient subgroups, including patient age and cytogenetic risk status (Figure 2).

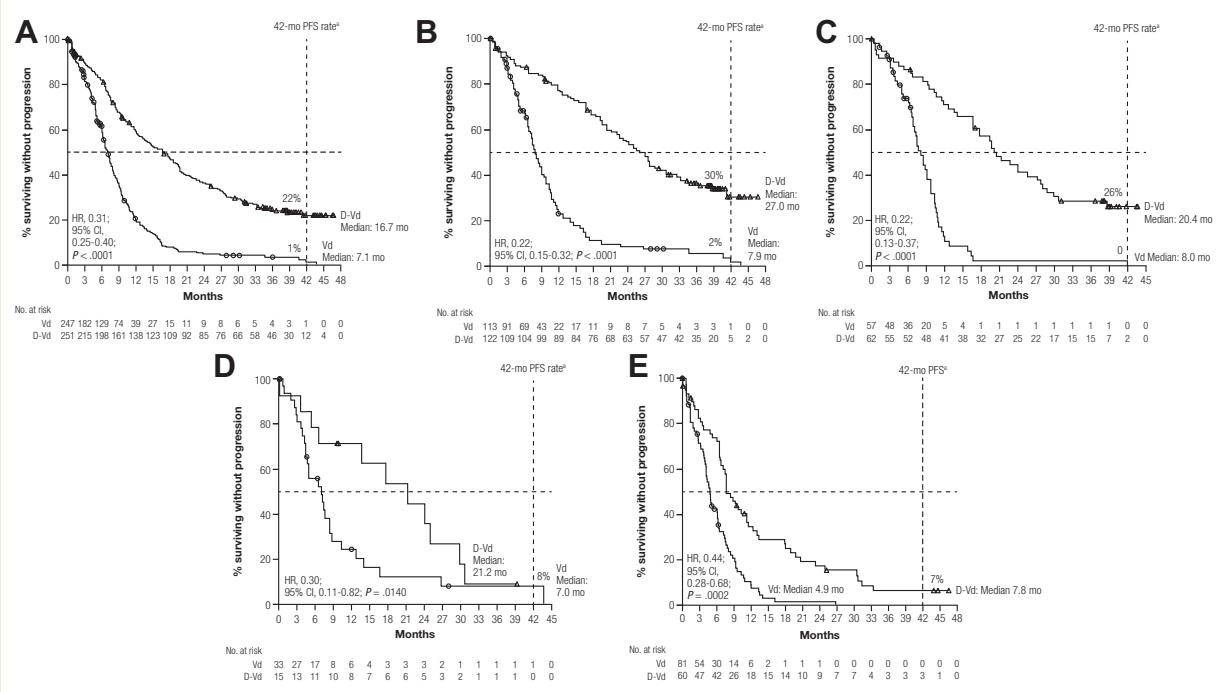
The 42-month PFS rates were 22% for D-Vd and 1% for Vd. For patients with 1 to 3 prior lines of therapy, median PFS was 18.0 months with D-Vd versus 7.3 months with Vd (HR, 0.31; 95% CI, 0.25-0.40; $P < .0001$). The ORR was significantly improved with D-Vd versus Vd in the ITT population (85% vs. 63%), as were rates of very good partial response or better (≥ VGPR, 63% vs. 29%) and CR or better (≥ CR, 30% vs. 10%; all $P < .0001$) (Table 2). These deep responses correlated with longer PFS, with patients with ≥ CR achieving a 42-month PFS rates of 53% for D-Vd and 10% for Vd. Time to first response (PR or better) was significantly more rapid for patients receiving D-Vd than Vd alone (median time to first response, 0.85 months D-Vd vs. 1.61 months Vd; HR, 1.88; 95% CI, 1.51-2.35; $P < .0001$).

For the subgroup of patients with 1 prior line of therapy, the median PFS was 27.0 months with D-Vd versus 7.9 months with Vd (HR, 0.22; 95% CI, 0.15-0.32; $P < .0001$) (Figure 1B). This PFS benefit was maintained regardless of whether the prior line of therapy included bortezomib (median 20.4 vs. 8.0 months; HR, 0.22; 95% CI, 0.13-0.37; $P < .0001$) (Figure 1C) or lenalidomide (median 21.2 vs. 7.0 months; HR, 0.30; 95% CI, 0.11-0.82; $P = .0140$) (Figure 1D). Response rates for patients with 1 prior line of therapy were also significantly higher for those receiving D-Vd compared with Vd, with an ORR of 92% versus 74%, a ≥ VGPR rate of 77% versus 42%, and a ≥ CR rate of 43% versus 15% (all $P < .001$) (Table 2). Similar to the ITT population, time to first response was significantly more rapid for patients receiving D-Vd than Vd alone (median time to first response, 0.82 months D-Vd vs. 1.48 months Vd; HR, 2.01; 95% CI, 1.47-2.74; $P < .0001$).

The PFS benefit derived from treatment with D-Vd compared with Vd was also maintained for patients who were refractory to lenalidomide in any prior line of therapy (median PFS, 7.8 months vs. 4.9 months; HR, 0.44; 95% CI, 0.28-0.68; $P = .0002$) (Figure 1E).

The deep responses observed in the D-Vd arm translated to significantly higher rates of MRD negativity at a $10^{-5}$ threshold, with 35 (14%) patients receiving D-Vd achieving MRD negativity at the time of clinical cutoff, compared with 4 (2%) patients receiving Vd ($P < .0001$) (Table 2). Increased rates of MRD negativity were also seen in the subgroup of patients who received 1 prior line of therapy, with 24 (20%) patients receiving D-Vd attaining MRD-negative status compared with 3 (3%) patients receiving Vd ($P < .0001$) (Table 2). Across treatment groups, patients achieving MRD negativity had prolonged PFS compared with patients who did not achieve MRD negativity (Figure 3). The median PFS was not estimable for MRD-negative patients receiving D-Vd and 37.6 months for patients receiving Vd; for patients who

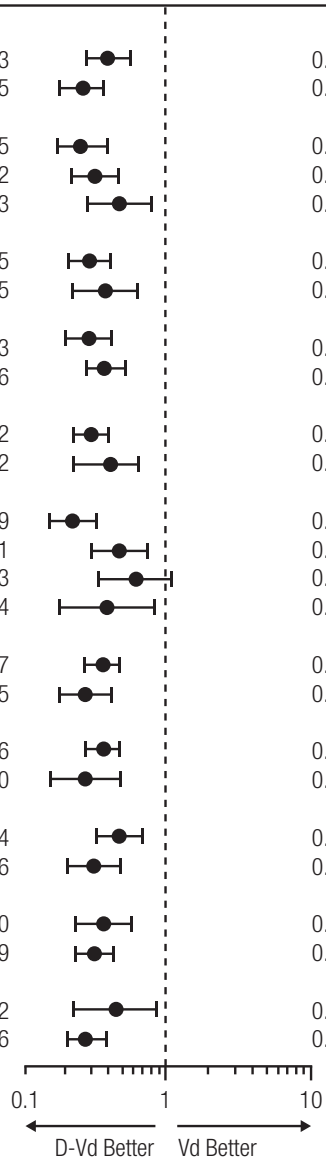
**Figure 1** PFS for the ITT Population (A); Patients Who Received 1 Prior Line of Therapy (B); PFS for Patients With 1 Prior Line of Therapy Who Were Treated With Bortezomib (C) or Lenalidomide (D); and Patients in the ITT Population Who Were Refractory to Lenalidomide (E)




Abbreviations: CI = confidence interval; D-Vd = daratumumab/bortezomib/dexamethasone; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival; Vd = bortezomib/dexamethasone.
[a]Kaplan-Meier estimates.

**Figure 2** PFS in Pre-specified Patient Subgroups

| | D-Vd *no. of progression events or deaths/total no.* | Vd *no. of progression events or deaths/total no.* | D-Vd *median progression-free survival (mo)* | Vd *median progression-free survival (mo)* | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| Age | | | | | |
| <65 years | 98/132 | 103/125 | 16.6 | 7.3 | 0.39 (0.28-0.54) |
| ≥65 years | 82/119 | 105/122 | 17.9 | 6.5 | 0.26 (0.18-0.37) |
| ISS disease stage | | | | | |
| I | 59/98 | 79/96 | 22.7 | 8.5 | 0.25 (0.17-0.38) |
| II | 76/94 | 88/100 | 14.7 | 6.2 | 0.32 (0.22-0.46) |
| III | 45/59 | 41/51 | 8.3 | 5.3 | 0.46 (0.28-0.76) |
| Type of measurable MM | | | | | |
| IgG | 93/125 | 127/138 | 17.8 | 6.5 | 0.28 (0.20-0.40) |
| Non-IgG | 48/61 | 49/58 | 19.4 | 7.5 | 0.37 (0.22-0.61) |
| ECOG performance score | | | | | |
| 0 | 77/106 | 97/116 | 17.8 | 7.3 | 0.28 (0.19-0.41) |
| ≥1 | 103/144 | 111/131 | 14.3 | 6.6 | 0.37 (0.27-0.51) |
| Baseline renal function (CrCl) | | | | | |
| >60 mL/min | 135/186 | 145/165 | 17.9 | 7.2 | 0.29 (0.22-0.38) |
| ≤60 mL/min | 42/57 | 61/70 | 13.1 | 6.2 | 0.37 (0.22-0.61) |
| Number of prior lines of therapy | | | | | |
| 1 | 76/122 | 98/113 | 27.0 | 7.9 | 0.22 (0.15-0.32) |
| 2 | 54/70 | 60/74 | 12.0 | 7.1 | 0.46 (0.30-0.72) |
| 3 | 31/37 | 28/32 | 8.8 | 5.3 | 0.60 (0.33-1.07) |
| >3 | 19/22 | 22/28 | 8.1 | 5.4 | 0.37 (0.17-0.80) |
| Prior bortezomib treatment | | | | | |
| Yes | 127/162 | 136/164 | 12.1 | 6.7 | 0.35 (0.26-0.45) |
| No | 53/89 | 72/83 | 27.6 | 7.5 | 0.26 (0.17-0.40) |
| Prior IMiD | | | | | |
| Yes | 132/179 | 165/198 | 13.1 | 6.6 | 0.35 (0.27-0.45) |
| No | 48/72 | 43/49 | 20.4 | 8.0 | 0.27 (0.15-0.46) |
| Refractory to IMiD | | | | | |
| Yes | 67/83 | 86/97 | 8.8 | 5.4 | 0.46 (0.31-0.66) |
| No | 65/96 | 79/101 | 19.7 | 7.6 | 0.30 (0.20-0.45) |
| Refractory to last line of prior therapy | | | | | |
| Yes | 61/76 | 72/85 | 9.3 | 5.0 | 0.36 (0.23-0.55) |
| No | 119/175 | 136/162 | 19.4 | 7.9 | 0.31 (0.23-0.41) |
| Cytogenetic profile[a] | | | | | |
| High risk[b] | 33/40 | 31/35 | 12.6 | 6.2 | 0.41 (0.21-0.83) |
| Standard risk | 98/141 | 117/140 | 16.6 | 6.6 | 0.26 (0.19-0.37) |




Abbreviations: CI = confidence interval; CrCl = creatinine clearance; D-Vd = daratumumab/bortezomib/dexamethasone; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; IgG = immunoglobulin G; IMiD = immunomodulatory drug; ISS = International Staging System; MM = multiple myeloma; PFS = progression-free survival; Vd = bortezomib/dexamethasone.
[a]Cytogenetic risk status by fluorescence in situ hybridization or karyotype testing. [b]High-risk patients had t(4;14), t(14;16), or del17p cytogenetic abnormalities by FISH or karyotyping.

did not achieve MRD negativity, the median PFS was 13.0 months and 6.8 months, respectively. Regardless of MRD status, patients receiving D-Vd experienced significantly prolonged PFS compared with those receiving Vd alone (MRD-negative: HR, 0.31; 95% CI, 0.10-1.01; $P = .041$; MRD-positive: HR, 0.40; 95% CI, 0.32-0.50; $P < .0001$).

Patients in the D-Vd arm had a significantly increased median time to subsequent therapy compared with patients in the Vd arm (ITT, 25.4 vs. 9.7 months; HR, 0.27; 95% CI, 0.21-0.35; $P < .0001$). A similar difference between treatment arms was observed for patients treated with 1 prior line of therapy (33.3 vs. 11.1 months; HR, 0.22; 95% CI, 0.15-0.32; $P < .0001$).

PFS2 was significantly prolonged with D-Vd compared with Vd in the ITT population (median 34.2 vs. 20.3 months; HR, 0.48; 95% CI, 0.38-0.61; $P < .0001$) (Figure 4A). In the ITT population, 42-month PFS2 rates were 42% and 14% for D-Vd and Vd,

**Table 2** Response and MRD-negativity Rates in the Overall Population and in Patients With 1 Prior Line of Therapy

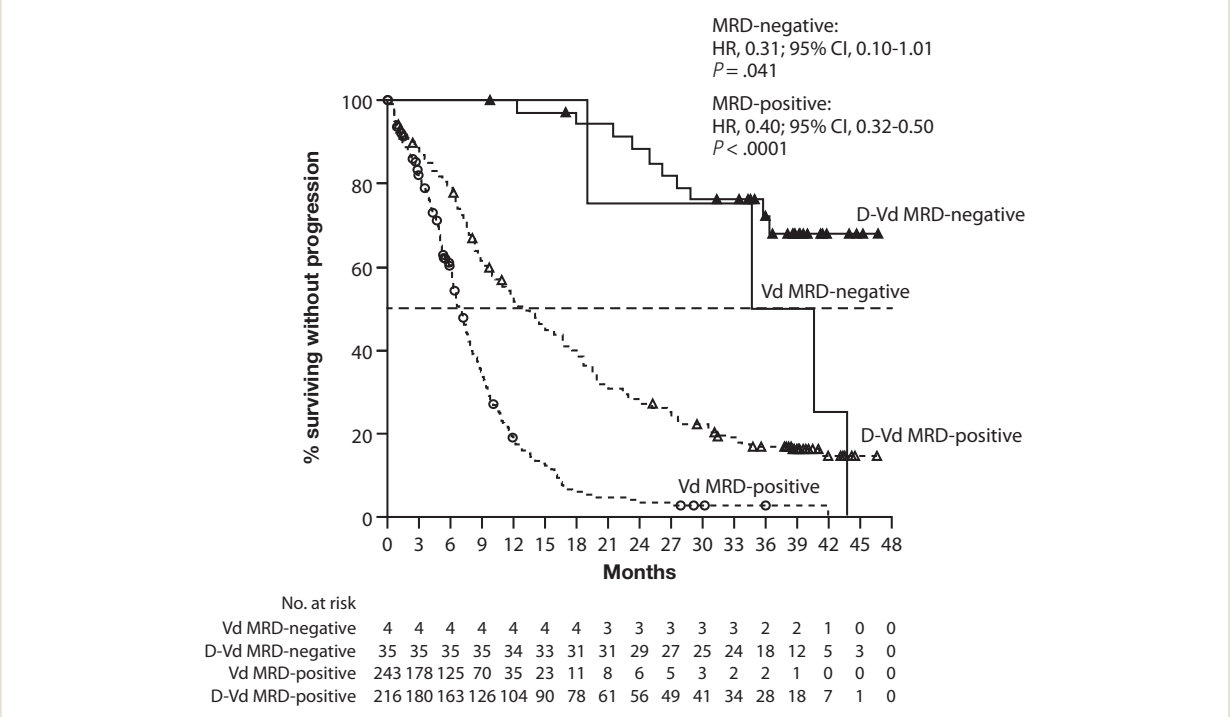
| | ITT Population | | | 1 Prior Line of Therapy Subgroup | | |
|---|---|---|---|---|---|---|
| | D-Vd | Vd | *P* Value | D-Vd | Vd | *P* Value |
| Response, n (%)[a] | n = 240 | n = 234 | | n = 119 | n = 109 | |
| ORR | 203 (85) | 148 (63) | < .0001 | 109 (92) | 81 (74) | .0007 |
| ≥ CR | 72 (30) | 23 (10) | < .0001 | 51 (43) | 16 (15) | < .0001 |
| sCR | 23 (10) | 6 (3) | | 17 (14) | 5 (5) | |
| CR | 49 (20) | 17 (7) | | 34 (29) | 11 (10) | |
| ≥ VGPR | 151 (63) | 68 (29) | < .0001 | 91 (77) | 46 (42) | < .0001 |
| VGPR | 79 (33) | 45 (19) | | 40 (34) | 30 (28) | |
| PR | 52 (22) | 80 (34) | | 18 (15) | 35 (32) | |
| MRD-negative ($10^{-5}$)[b] | n = 251 | n = 247 | | n = 122 | n = 113 | |
| n (%) | 35 (14) | 4 (2) | < .000001 | 24 (20) | 3 (3) | .000025 |

Abbreviations: CR = complete response; D-Vd = daratumumab/bortezomib/dexamethasone; ITT = intent-to-treat; MRD = minimal residual disease; ORR = overall response rate; PR = partial response; sCR = stringent complete response; Vd = bortezomib/dexamethasone; VGPR = very good partial response.
[a]Response-evaluable population.
[b]ITT population.

respectively. Similar PFS2 benefits were observed for patients in the 1 prior line of therapy subgroup (median not reached vs. 23.3 months; HR, 0.35; 95% CI, 0.24-0.51; $P < .0001$), and 42-month PFS2 rates were 54% versus 19%, respectively (Figure 4B). PFS2 was significantly prolonged in the subgroup of patients in the Vd group who received daratumumab monotherapy as their next line of therapy at disease progression (n = 40) compared with other patients in the Vd group (n = 207) who did not switch to daratumumab monotherapy or switched to daratumumab monotherapy but not as the first line of subsequent anticancer therapy (median 31.6 vs. 17.2 months; HR, 0.43; 95% CI, 0.27-0.66; $P < .0001$).

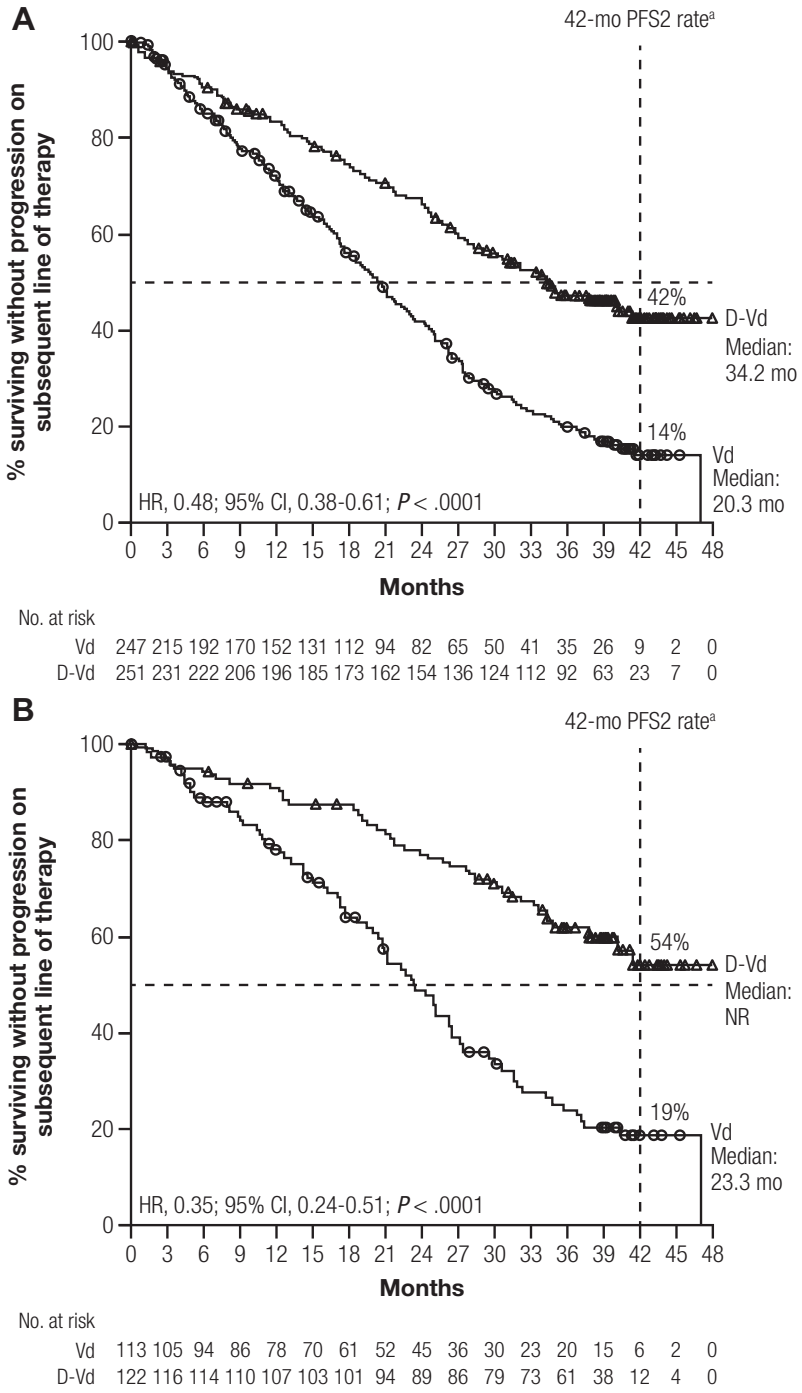
Median overall survival (OS) has not been reached. At the time of analysis, 102 deaths in the D-Vd arm and 119 deaths in the Vd arm were observed. For patients with 1 prior line of treatment, 35 deaths in the D-Vd arm and 51 deaths in the Vd arm have occurred. Follow-up for OS is ongoing.

**Figure 3** PFS by MRD Status for the ITT Population




Abbreviations: CI = confidence interval; D-Vd = daratumumab/bortezomib/dexamethasone; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival; MRD = minimal residual disease; Vd = bortezomib/dexamethasone.

**Figure 4** PFS2 for the ITT Population (A) and Patients Who Received 1 Prior Line of Therapy Who Were Treated With D-Vd or Vd (B)




Abbreviations: CI = confidence interval; D-Vd = daratumumab/bortezomib/dexamethasone; HR = hazard ratio; ITT = intent-to-treat; PFS2 = progression-free survival on the next line of therapy; Vd = bortezomib/dexamethasone.
[a]Kaplan-Meier estimates.

### *Safety*

The safety population included 243 patients who received D-Vd and 237 patients who received Vd. With extended follow-up, no new safety concerns were observed compared with previous analyses[9,24] (Table 3). The most common (≥ 10%) grade 3/4 treatment-emergent adverse events (TEAEs) in the D-Vd versus Vd arms were thrombocytopenia (46% vs. 33%), anemia (16% vs. 16%), and pneumonia (10% vs. 10%). Rates of grade 3/4 infection

were higher for D-Vd versus Vd (29% vs. 19%); however, after adjusting for exposure, grade 3/4 infection events per patient-year were lower with D-Vd versus Vd (0.26 vs. 0.68). Rates of discontinuation owing to TEAEs were similar for D-Vd versus Vd (10% vs. 9%).

With longer follow-up, second primary malignancies (cutaneous, invasive, and hematologic) were reported in 14 (6%) patients in the D-Vd arm (4 new cases since the previous analysis) and 5 (2%) patients in the Vd arm (4 new cases since the previous analysis). No cancer type was predominant for second primary malignancies in either treatment arm.

## Discussion

With greater than 3 years of median follow-up, D-Vd maintains significant PFS and ORR benefits compared with Vd alone in patients with RRMM. The safety profile remains consistent after 40 months of follow-up, emphasizing the tolerability and predictability of daratumumab monotherapy following 8 cycles of D-Vd. Although the PFS benefit of D-Vd over Vd was observed regardless of the number of prior lines of therapy, the benefit was more pronounced in patients who had received 1 prior line of treatment, and was maintained regardless of whether the first-line regimen included bortezomib or lenalidomide. D-Vd also improved outcomes versus Vd alone for the increasingly clinically important group of patients who were refractory to lenalidomide in any prior line of treatment.[3]

Responses to therapy with D-Vd were deep and durable overall, and were more pronounced for patients with 1 prior line of treatment, with 92% of patients achieving at least a PR (43% with $\geq$ CR) and 20% achieving MRD negativity at a $10^{-5}$ sensitivity threshold. These findings in patients who relapsed after or were refractory to their first line of treatment suggest a need to integrate effective therapies early in the course of treatment to drive patients toward MRD negativity, which has been shown to correlate with favorable long-term outcomes in NDMM.[26,27] In this study of patients with RRMM, MRD negativity was also associated with prolonged PFS irrespective of treatment, although the majority of MRD-negative patients had received D-Vd. Achieving deep responses, such as MRD negativity, is an important treatment goal but, as seen in this study, some patients will eventually relapse. The durability of an MRD-negative response is an important factor in determining long-term outcomes.[25] Preliminary data from the CASTOR study identified a cohort of patients who achieved MRD negativity that sustained this response for over 6 months and in some cases for more than 12 months.[28] In these patients, sustained MRD was associated with improved PFS and OS. It should be noted, however, that this largely lenalidomide-naive patient population does not reflect the increasingly common group of patients who received lenalidomide in the first line of therapy observed in clinical practice.

Following disease progression, patients who received D-Vd had a significantly prolonged PFS2 compared with those who received Vd, despite 81 patients in the Vd group receiving daratumumab monotherapy after disease progression. PFS2 was significantly prolonged in the 40 patients in the Vd group who received daratumumab monotherapy as their first subsequent therapy after disease progression compared with those who did not switch to daratumumab or who switched to daratumumab after additional subsequent therapy (not as the first line of subsequent therapy), suggesting that daratumumab monotherapy is superior to other salvage therapies following progression on Vd. Although survival data remain immature in this study, PFS2 is a recommended surrogate endpoint for OS,[29] and these PFS2 data suggest there may be a survival benefit.

**Table 3** Most Common (> 20% of Patients) and Grade 3/4 (> 5% of Patients) TEAEs in the Safety Population

| | All Grades | | Grade 3/4 | |
|---|---|---|---|---|
| TEAE, n (%) | D-Vd (n = 243) | Vd (n = 237) | D-Vd (n = 243) | Vd (n = 237) |
| **Hematologic** | | | | |
| Thrombocytopenia | 145 (60) | 105 (44) | 112 (46) | 78 (33) |
| Anemia | 71 (29) | 75 (32) | 38 (16) | 38 (16) |
| Neutropenia | 48 (20) | 23 (10) | 33 (14) | 11 (5) |
| Lymphopenia | 32 (13) | 9 (4) | 24 (10) | 6 (3) |
| **Non-hematologic** | | | | |
| Peripheral sensory neuropathy | 121 (50) | 90 (38) | 11 (5) | 16 (7) |
| Upper respiratory tract infection | 85 (35) | 43 (18) | 6 (3) | 1 (0.4) |
| Diarrhea | 86 (35) | 53 (22) | 9 (4) | 3 (1) |
| Cough | 71 (29) | 30 (13) | 0 | 0 |
| Constipation | 54 (22) | 38 (16) | 0 | 2 (0.8) |
| Fatigue | 55 (23) | 58 (25) | 12 (5) | 8 (3) |
| Back pain | 53 (22) | 24 (10) | 6 (3) | 3 (1) |
| Pneumonia | 38 (16) | 31 (13) | 25 (10) | 24 (10) |
| Hypertension | 24 (10) | 8 (3) | 16 (7) | 2 (0.8) |

Abbreviations: D-Vd = daratumumab/bortezomib/dexamethasone; TEAE = treatment-emergent adverse event; Vd = bortezomib/dexamethasone.

The safety profile of D-Vd remains consistent after extended follow-up, during which a substantial number of patients continued to receive daratumumab monotherapy. Infection rates adjusted for exposure reveal that daratumumab does not increase the rates of infection. The results observed with extended follow-up suggest no cumulative toxicity, and these findings highlight the tolerability of daratumumab monotherapy used as maintenance treatment following 8 cycles of D-Vd. Rates of second primary malignancies were consistent with rates observed for patients with RRMM overall, and no notable increases were observed since the previous analysis of CASTOR.[9] A concern of adding a new agent to doublet regimens is that this may place an additional burden on patients. However, in an earlier update of the CASTOR study, it was reported that adding daratumumab to Vd does not worsen health-related quality of life.[9]

The outcomes of patients with RRMM treated with D-Vd compare favorably with other clinical trials in this patient population. In a subgroup analysis of the phase III ENDEAVOR study of carfilzomib-dexamethasone (Kd) versus Vd, patients with 1 prior line of treatment achieved a median PFS of 22.2 months versus 10.1 months, respectively (HR, 0.45; 95% CI, 0.33-0.61; $P < .0001$) after approximately 11 months of follow-up.[30] A randomized phase II study of SLAMF7-targeted monoclonal antibody elotuzumab in combination with Vd (Elo-Vd) versus Vd alone demonstrated a median PFS of 9.7 months with Elo-Vd versus 6.9 months with Vd after a median follow-up of 15.9 and 11.7 months, respectively.[7] In the phase III OPTIMISMM trial of pomalidomide plus Vd versus Vd alone in lenalidomide-exposed patients, the median PFS was 11.2 months versus 7.1 months after a median follow-up of 16 months (HR, 0.61; 95% CI, 0.49-0.77; $P < .0001$) in the ITT population. For patients with 1 prior line of therapy, the median PFS was 20.7 months versus 11.6 months (HR, 0.54; 95% CI, 0.36-0.82; $P = .0027$).[10] As depth and duration of response to treatment decrease with each subsequent line of therapy for patients with MM, and as many patients do not proceed to further treatment, there remains an unmet need for effective therapies that can be administered early in the treatment course.[31] Another daratumumab-containing regimen has been shown to provide clinical benefit when used earlier in the treatment of RRMM: after 25.4 months of median follow-up in the phase III POLLUX study, the median PFS was not reached for daratumumab plus lenalidomide and dexamethasone versus a median PFS of 19.6 months with lenalidomide and dexamethasone alone in patients with 1 prior line of treatment.[18]

The combination of daratumumab plus Vd also was efficacious in patients who were refractory to lenalidomide in prior treatment lines. Daratumumab in combination with a different PI (carfilzomib) and dexamethasone (D-Kd) has also shown a clinical benefit in lenalidomide-refractory patients. In the phase Ib MMY1001 study, in a subgroup of 51 lenalidomide-refractory patients with a median of 2 prior lines of treatment, the 12-month PFS rate was 69%.[32] A phase III study of D-Kd versus Kd (CANDOR; NCT03158688) is further evaluating this combination in patients with RRMM with 1 to 3 prior lines of therapy. Daratumumab plus pomalidomide and dexamethasone (D-Pd) is also an effective regimen in RRMM and is approved in the United States.[33,34] A European Myeloma Network phase III study (APOLLO) is evaluating D-Pd compared with Pd alone in patients with RRMM previously treated with a PI or an IMiD (NCT03180736). Patients with 1 prior line of treatment are required to be refractory to lenalidomide. These studies will provide further information on the efficacy of daratumumab-based combinations for the treatment of patients who are refractory to lenalidomide after their first line of therapy.

## Conclusion

With extended follow-up, significant improvements in PFS, ORR, and MRD negativity were observed for patients with RRMM treated with D-Vd versus Vd alone, and were especially pronounced in patients with 1 prior line of therapy. No new safety concerns were observed, supporting the tolerability and predictability of daratumumab monotherapy used as maintenance treatment.

### *Clinical Practice Points*

- New treatment options are required for patients with MM, as depth and duration of response decrease with subsequent lines of therapy.
- D-Vd is a widely used triplet regimen for the treatment of patients who have relapsed after 1 or more prior lines of therapy. Approval was based on the phase III CASTOR study.
- The CASTOR study is ongoing, and, after an extended follow-up of 40.0 months, D-Vd showed improved efficacy outcomes (including PFS, ORR, and MRD-negativity rate) compared with Vd alone.
- In the approved regimen, patients discontinue Vd after 8 cycles and remain on daratumumab monotherapy. No new safety concerns were observed for daratumumab monotherapy with extended follow-up, and rates of discontinuation owing to TEAEs remain low.
- Greater improvement in response was observed in patients with 1 prior line of therapy. Outcomes were also significantly improved in patients who were refractory to lenalidomide, a subset of patients that physicians are increasingly encountering owing to the use of this IMiD in frontline treatment.

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## Disclosure

M.-V. Mateos consulted for Janssen, Celgene, GlaxoSmithKline, AbbVie, Takeda, and Amgen; received honoraria from Janssen, Celgene, Takeda, and Amgen; and served on advisory committees for Celgene, Janssen, Takeda, Amgen, GlaxoSmithKline,

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