

Overall Survival With Daratumumab, Bortezomib, and Dexamethasone in Previously Treated Multiple Myeloma (CASTOR): A Randomized, Open-Label, Phase III Trial

Pieter Sonneveld, MD, PhD¹; Asher Chanan-Khan, MD²; Katja Weisel, MD³; Ajay K. Nooka, MD⁴; Tamas Masszi, MD⁵; Meral Beksac, MD⁶; Ivan Spicka, MD, PhD⁷; Vania Hungria, MD⁸; Markus Munder, MD⁹; Maria-Victoria Mateos, MD, PhD¹⁰; Tomer M. Mark, MD¹¹; Mark-David Levin, MD, PhD¹²; Tahamtan Ahmadi, MD¹³; Xiang Qin, MS¹⁴; Wendy Garvin Mayo, MSN¹⁵; Xue Gai, MMed¹⁶; Jodi Carey, BSN¹⁴; Robin Carson, MD¹⁴; and Andrew Spencer, MD¹⁷

PURPOSE At the primary analysis of CASTOR (median follow-up, 7.4 months), daratumumab plus bortezomib and dexamethasone (D-Vd) significantly prolonged progression-free survival versus bortezomib and dexamethasone (Vd) alone in relapsed or refractory multiple myeloma (RRMM). We report updated efficacy and safety results at the final analysis for overall survival (OS).

METHODS CASTOR was a multicenter, randomized, open-label, phase III study during which eligible patients with ≥ 1 line of prior therapy were randomly assigned to Vd (up to eight cycles) with or without daratumumab (until disease progression). After positive primary analysis and protocol amendment, patients receiving Vd were offered daratumumab monotherapy after disease progression.

RESULTS At a median (range) follow-up of 72.6 months (0.0-79.8), significant OS benefit was observed with D-Vd (hazard ratio, 0.74; 95% CI, 0.59 to 0.92; $P = .0075$). Median OS was 49.6 months with D-Vd versus 38.5 months with Vd. Prespecified subgroup analyses demonstrated an OS advantage with D-Vd versus Vd for most subgroups, including patients age ≥ 65 years and patients with one or two prior lines of therapy, International Staging System stage III disease, high-risk cytogenetic abnormalities, and prior bortezomib treatment. The most common ($\geq 10\%$) grade 3/4 treatment-emergent adverse events with D-Vd versus Vd were thrombocytopenia (46.1% v 32.9%), anemia (16.0% v 16.0%), neutropenia (13.6% v 4.6%), lymphopenia (10.3% v 2.5%), and pneumonia (10.7% v 10.1%).

CONCLUSION D-Vd significantly prolonged OS in patients with RRMM, with the greatest OS benefit observed in patients with one prior line of therapy. To our knowledge, our results, together with the OS benefit observed with daratumumab plus lenalidomide and dexamethasone in the phase III POLLUX study, demonstrate for the first time an OS benefit with daratumumab-containing regimens in RRMM (ClinicalTrials.gov identifier: NCT02136134 [CASTOR]).

J Clin Oncol 41:1600-1609. © 2022 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License

ASSOCIATED CONTENT

Appendix Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 27, 2022 and published at ascopubs.org/journal/jco on November 22, 2022: DOI <https://doi.org/10.1200/JCO.21.02734>

INTRODUCTION

Daratumumab is a human IgG κ monoclonal antibody targeting CD38 with a direct on-tumor¹⁻⁴ and immunomodulatory⁵⁻⁷ mechanism of action, demonstrating greater cytotoxicity toward multiple myeloma (MM) cells ex vivo compared with analogs of other CD38 antibodies.⁸ Daratumumab induces higher levels of complement-dependent cytotoxicity, similar levels of antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis, and, in the presence of Fc receptor crosslinking, which occurs physiologically in vivo, daratumumab elicits similar levels of cell death.⁸ In phase III studies in newly

diagnosed MM (NDMM) and relapsed or refractory MM (RRMM), the addition of daratumumab to standard-of-care regimens significantly reduced the risk of disease progression or death and achieved deep and durable responses, including significantly higher complete response or better (\geq CR) rates and minimal residual disease (MRD)-negativity rates, versus standard of care alone.⁹⁻¹⁴ On the basis of these results, daratumumab is approved in combination with standard-of-care regimens for patients with RRMM or NDMM.^{15,16}

At the primary analysis of the phase III CASTOR study (median follow-up, 7.4 months), daratumumab plus bortezomib and dexamethasone (D-Vd) significantly

CONTEXT

Key Objective

To report updated efficacy and safety results, including overall survival (OS), from the phase III CASTOR study of daratumumab, bortezomib, and dexamethasone (D-Vd) in patients with relapsed or refractory multiple myeloma after approximately 6 years of follow-up.

Knowledge Generated

At a median follow-up of 72.6 months, D-Vd significantly prolonged OS, with a 26% reduction in the risk of death versus bortezomib and dexamethasone alone (median, 49.6 v 38.5 months, respectively; hazard ratio, 0.74; 95% CI, 0.59 to 0.92; $P = .0075$). Prespecified subgroup analyses showed OS improvement with D-Vd versus bortezomib and dexamethasone across most patient subgroups, with the greatest benefit observed in patients with one prior line of therapy.

Relevance

To our knowledge, these results, together with the OS benefit observed with daratumumab plus lenalidomide and dexamethasone in the phase III POLLUX study, demonstrate for the first time an OS benefit with daratumumab-containing regimens in relapsed or refractory multiple myeloma, with the greatest benefit observed in patients with one prior line of therapy.

prolonged progression-free survival (PFS; hazard ratio [HR], 0.39; 95% CI, 0.28 to 0.53; $P < .001$) and induced higher rates of deeper responses than bortezomib and dexamethasone (Vd) alone in patients with RRMM.¹⁷ After longer follow-up (median, 19.4 months), D-Vd reduced the risk of disease progression or death by 69% (median PFS, 16.7 v 7.1 months; HR, 0.31; 95% CI, 0.24 to 0.39; $P < .0001$) and responses deepened, resulting in higher \geq CR rates (28.8% v 9.8%; $P < .0001$) and MRD-negativity rates (10^{-5} sensitivity; 11.6% v 2.4%; $P = .000034$) versus Vd.¹⁸ In the most recent analysis of the study at a median follow-up of 50.2 months, D-Vd continued to demonstrate significant efficacy benefits versus Vd alone, inducing deep and more durable responses and improved MRD-negativity rates.¹⁹ Efficacy benefits were most pronounced in patients who received one prior line of therapy, regardless of prior treatment with lenalidomide.

We report updated efficacy and safety results at the time of the final overall survival (OS) analysis of CASTOR after approximately 6 years of follow-up.

METHODS

Trial Design and Oversight

CASTOR (ClinicalTrials.gov identifier: [NCT02136134](https://clinicaltrials.gov/ct2/show/study/NCT02136134)) was a multicenter, randomized, open-label, active-controlled, phase III study in patients with RRMM. The study design has been published previously.¹⁷ Eligible patients had progressive disease per International Myeloma Working Group criteria^{20,21} during or after completion of their last regimen, received ≥ 1 prior line of therapy, and had a partial response or better to ≥ 1 previous line of therapy.¹⁷ Patients refractory to bortezomib or another proteasome inhibitor were ineligible. The trial protocol was approved by independent ethics committees or institutional review boards at each center. Patients provided written informed consent, and the trial was

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

Random Assignment and Study Treatment

Patients were randomly assigned (1:1) to D-Vd or Vd and stratified by International Staging System disease stage (I, II, or III), number of prior lines of therapy (1 v 2 or 3 v > 3), and previous bortezomib treatment (yes v no). All patients received up to eight cycles (21 days/cycle) of bortezomib (1.3 mg/m² subcutaneously once on days 1, 4, 8, and 11) and dexamethasone (20 mg orally or intravenously once on days 1, 2, 4, 5, 8, 9, 11, and 12). For patients in the D-Vd group, daratumumab (16 mg/kg intravenously) was administered once weekly (days 1, 8, and 15) in cycles 1-3, once every 3 weeks (on day 1) in cycles 4-8, and once every 4 weeks thereafter until disease progression or unacceptable toxicity. After positive primary analysis and protocol amendment, patients receiving Vd were offered daratumumab monotherapy after disease progression or after a washout period if they already experienced disease progression and were receiving subsequent therapy.

End Points and Assessments

PFS was the primary efficacy end point.¹⁷ Secondary end points included time to disease progression, overall response rate, MRD negativity, and OS. Exploratory secondary analyses examined subpopulations by number of lines of therapy, prior treatment exposure, and cytogenetic risk assessed by next-generation sequencing, as described previously.¹⁸ Tumor response and disease progression were assessed using a validated computerized algorithm in accordance with International Myeloma Working Group response criteria.^{20,21} MRD was assessed using bone marrow aspirate samples and evaluated via next-generation sequencing using the clonoSEQ assay (v.2.0; Adaptive

Biotechnologies, Seattle, WA). MRD was assessed in patients with suspected CR, in patients who achieved CR (including patients with very good partial response and suspected daratumumab interference) at cycle 9 day 1 and cycle 15 day 1 (6 months after the end of the Vd backbone), and every 12 months (\pm 3 months) after CR until the end of treatment. Patients were considered to be MRD-positive if they had an MRD-positive test result or had no MRD assessment. Cytogenetic risk was evaluated locally using local fluorescence in situ hybridization or karyotyping. High-risk patients had t(4;14), t(14;16), or del17p cytogenetic abnormalities.

Statistical Analysis

Unless otherwise specified, efficacy analyses were based on the intention-to-treat population. Time-to-event end points were compared between groups using a stratified log-rank test. HRs and 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The Kaplan–Meier method was used to estimate the distributions. Binary end points, including overall response rate, were assessed using the stratified Cochran–Mantel–Haenszel test. MRD-negativity rates were compared using Fisher's exact test.

RESULTS

Patients

Patients were recruited between September 4, 2014, and September 24, 2015. In total, 498 patients were randomly assigned to D-Vd ($n = 251$) or Vd ($n = 247$; Fig 1). Patient demographics and baseline clinical characteristics were generally well balanced and have been published previously.¹⁷ Median (range) age was 64 (30–88) years, and median (range) number of prior lines of therapy was 2 (1–10) (Appendix Table A1, online only). Prior therapies included bortezomib (65.5%), thalidomide (49.4%), lenalidomide (42.0%), and both a proteasome inhibitor and an immunomodulatory drug (48.4%).

A total of 87 Vd patients subsequently received single-agent daratumumab after disease progression (or after a washout period if they already experienced disease progression and were receiving subsequent therapy), provided per study protocol. The median (range) number of daratumumab cycles received during monotherapy was 11.0 (1–63), and median (range) duration of daratumumab monotherapy was 9.2 months (0.2–57.1). An additional 38 patients received daratumumab as subsequent therapy not provided in the study.

Efficacy

At the clinical cutoff (June 28, 2021), at a median (range) follow-up of 72.6 months (0.0–79.8), a total of 148 (59.0%) of 251 patients in the D-Vd group and 171 (69.2%) of 247 patients in the Vd group died. The HR for death for D-Vd compared with Vd was 0.74 (95% CI, 0.59 to 0.92;

$P = .0075$; Fig 2A), crossing the prespecified stopping boundary of $P = .0323$ and representing a 26% reduction in the risk of death. Median OS was 49.6 months (95% CI, 42.2 to 62.3) for D-Vd versus 38.5 months (95% CI, 31.2 to 46.2) for Vd. Prespecified subgroup analyses showed OS benefit for patients in the D-Vd group versus patients in the Vd group across most patient subgroups, including patients age ≥ 65 years, patients who have received one or two prior lines of therapy, and patients with poor prognosis, such as those with advanced-stage disease (International Staging System stage III), high-risk cytogenetic abnormalities, and prior bortezomib treatment (Fig 3). It is noteworthy that OS benefit was most pronounced in patients who received one prior line of therapy (HR, 0.56; 95% CI, 0.39 to 0.80).

Significantly higher MRD-negativity rates (10^{-5} sensitivity threshold) were achieved with D-Vd versus Vd (15.1% v 1.6%; $P < .0001$). MRD negativity was associated with improved OS, regardless of treatment group (Fig 4).

A total of 161 (66.3%) of 243 patients in the D-Vd group and 200 (84.4%) of 237 patients in the Vd group received subsequent therapy; median (range) number of subsequent lines of therapy was 2 (1–9) and 3 (1–10), respectively. Median time to subsequent therapy was significantly increased in the D-Vd arm versus the Vd arm (25.4 v 9.7 months; HR, 0.27; 95% CI, 0.21 to 0.34; $P < .0001$). The most common subsequent anticancer therapies included dexamethasone (59.3%), lenalidomide (39.9%), cyclophosphamide (28.0%), pomalidomide (23.0%), carfilzomib (21.0%), and bortezomib (19.8%) in the D-Vd arm and dexamethasone (66.2%), daratumumab (52.7%), lenalidomide (46.0%), cyclophosphamide (33.8%), pomalidomide (32.1%), carfilzomib (24.9%), and bortezomib (23.2%) in the Vd arm. PFS2 (defined as the time from random assignment to progression on the next line of therapy) was significantly prolonged with D-Vd versus Vd (median, 37.7 v 19.9 months; HR, 0.43; 95% CI, 0.34 to 0.54; $P < .0001$; Fig 2B). The most common first subsequent therapy was lenalidomide and dexamethasone (Rd) in the D-Vd arm (23.9%) and daratumumab monotherapy (22.4%) or Rd (18.9%) in the Vd arm (Appendix Table A2, online only). Median PFS for patients who started first line of subsequent therapy was 13.2 months (95% CI, 10.1 to 15.4) in the D-Vd group and 9.2 months (95% CI, 7.4 to 10.6) in the Vd group.

After disease progression, median (range) time to crossover to daratumumab subsequent therapy for patients in the Vd arm was 20.5 months (5.7–68.3). Of the 87 patients in the Vd group who received subsequent daratumumab monotherapy after disease progression, provided per study protocol, 35 (40.2%) are still alive; median OS is 63.4 months (95% CI, 51.2 to 72.4).

Safety

With longer follow up, no new safety concerns were reported (Table 1). The most common ($\geq 10\%$) grade 3/4 treatment-emergent adverse events (TEAEs) with D-Vd versus Vd were

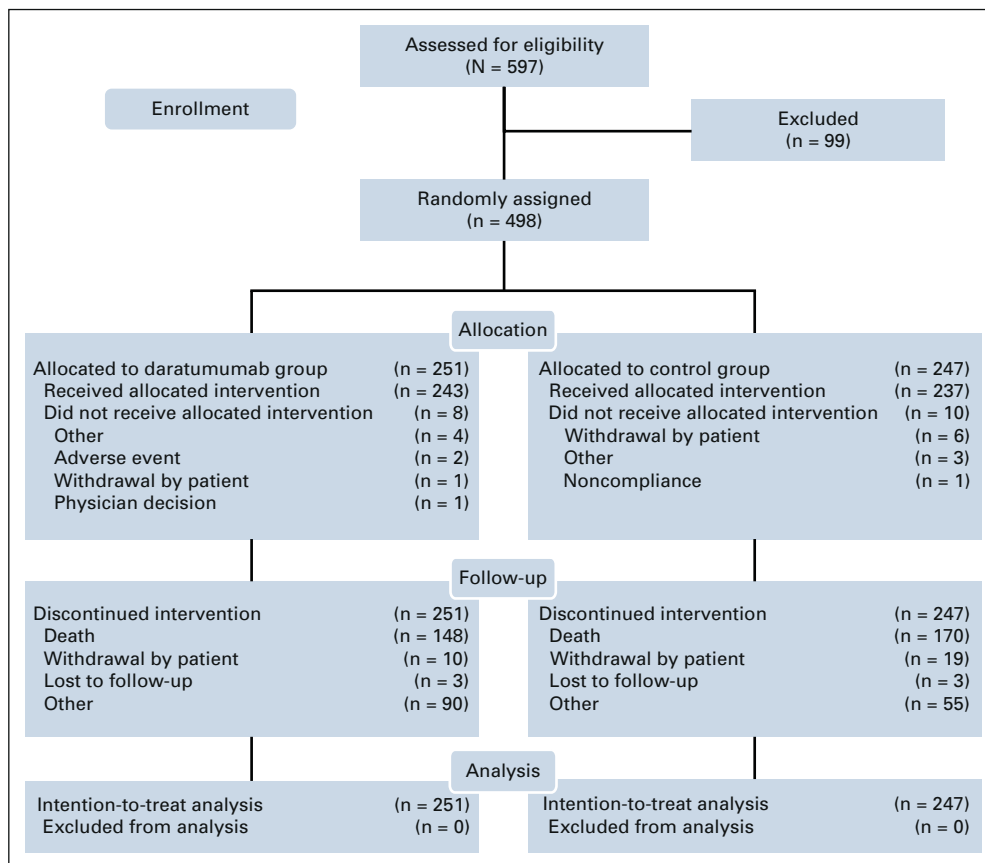


FIG 1. CONSORT diagram for CASTOR.

thrombocytopenia (46.1% v 32.9%), anemia (16.0% v 16.0%), neutropenia (13.6% v 4.6%), lymphopenia (10.3% v 2.5%), and pneumonia (10.7% v 10.1%). Grade 3/4 infections occurred in 72 (29.6%) patients in the D-Vd arm and 45 (19.0%) patients in the Vd arm. Serious TEAEs occurred in 134 (55.1%) patients who received D-Vd and 81 (34.2%) patients who received Vd, the most common being pneumonia (10.7% and 10.1%, respectively). The percentage of patients with TEAEs leading to discontinuation remained low and similar between groups (D-Vd, 10.7%; Vd, 9.3%). Seven (2.9%) patients in the D-Vd arm and 5 (2.1%) patients in the Vd arm discontinued treatment because of infections.

TEAEs that resulted in death were reported in 17 (7.0%) patients in the D-Vd group and 14 (5.9%) patients in the Vd group. The most frequent TEAEs with an outcome of death were pneumonia (0.8% each) and general physical health deterioration (0.4% v 1.3%, respectively). Three patients died during the study due to COVID-19 disease (one in the D-Vd group and two in the Vd group). With extended follow up, the incidence of second primary malignancies (cutaneous, invasive, and hematologic) was 20 (8.2%) patients in the D-Vd arm (6 new cases since the 3-year follow-up analysis) and 5 (2.1%) patients in the Vd arm (no new cases). There was no predominant cancer type for second

primary malignancies in either treatment arm. When adjusted for exposure to study treatment, the rate of second primary malignancies was similar between the D-Vd (0.35 events per 100 patient-months at risk) and Vd (0.46 events per 100 patient-months at risk) groups.

DISCUSSION

It is our understanding that these long-term results from the CASTOR study represent the first OS data with daratumumab in the RRMM population and provide further support of a survival advantage with a daratumumab-containing regimen in multiple myeloma.^{10,22} For the first time to our knowledge, the combination of daratumumab and a standard-of-care regimen significantly improved OS in patients with RRMM. The addition of daratumumab to Vd prolonged OS in patients with RRMM, with a 26% reduction in the risk of death versus Vd alone after a median follow-up of 72.6 months. The OS curves separated at approximately 8 months and continued to separate with time. The final MRD-negativity rate analysis results (median follow-up, 72.6 months) were consistent with those reported in the updated analysis (median follow-up, 19.4 months).¹⁸ OS was improved in patients who achieved MRD negativity compared with patients who were MRD-positive. It appears that the superiority in OS is derived from patients who achieved MRD negativity in the D-Vd group because OS was similar in

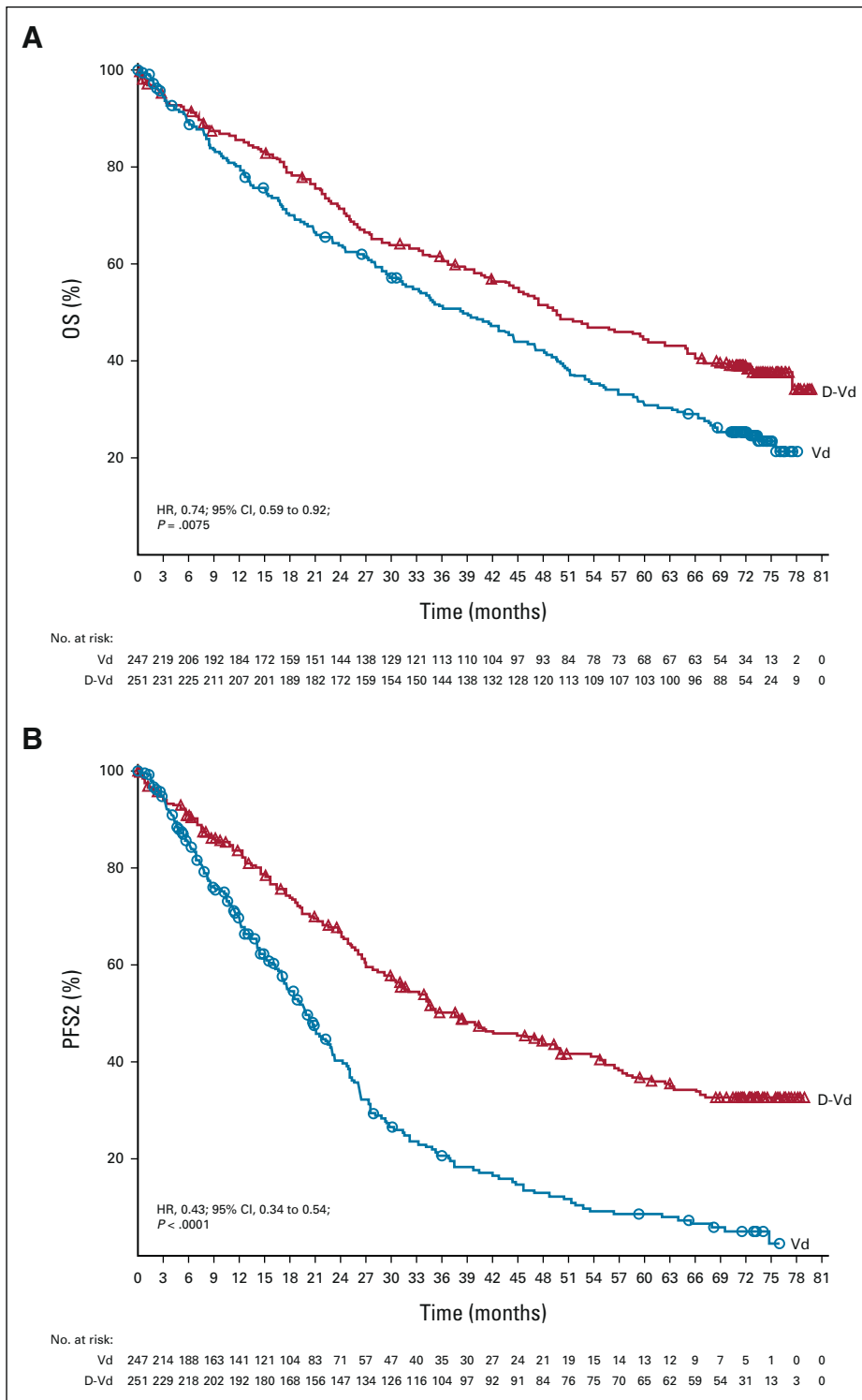


FIG 2. Kaplan–Meier estimates of (A) OS and (B) PFS2 in the ITT population, which included all patients who underwent random assignment. D-Vd, daratumumab, bortezomib, and dexamethasone; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS2, progression-free survival on the subsequent line of therapy; Vd, bortezomib and dexamethasone.

the D-Vd and Vd groups in patients who were MRD-positive. This further reinforces the importance of achieving MRD negativity. A significant PFS2 benefit was maintained for the

D-Vd group, with a 57% reduction in the risk of disease progression or death. These results build on the significant PFS benefit previously reported with D-Vd, with a 69% reduction in

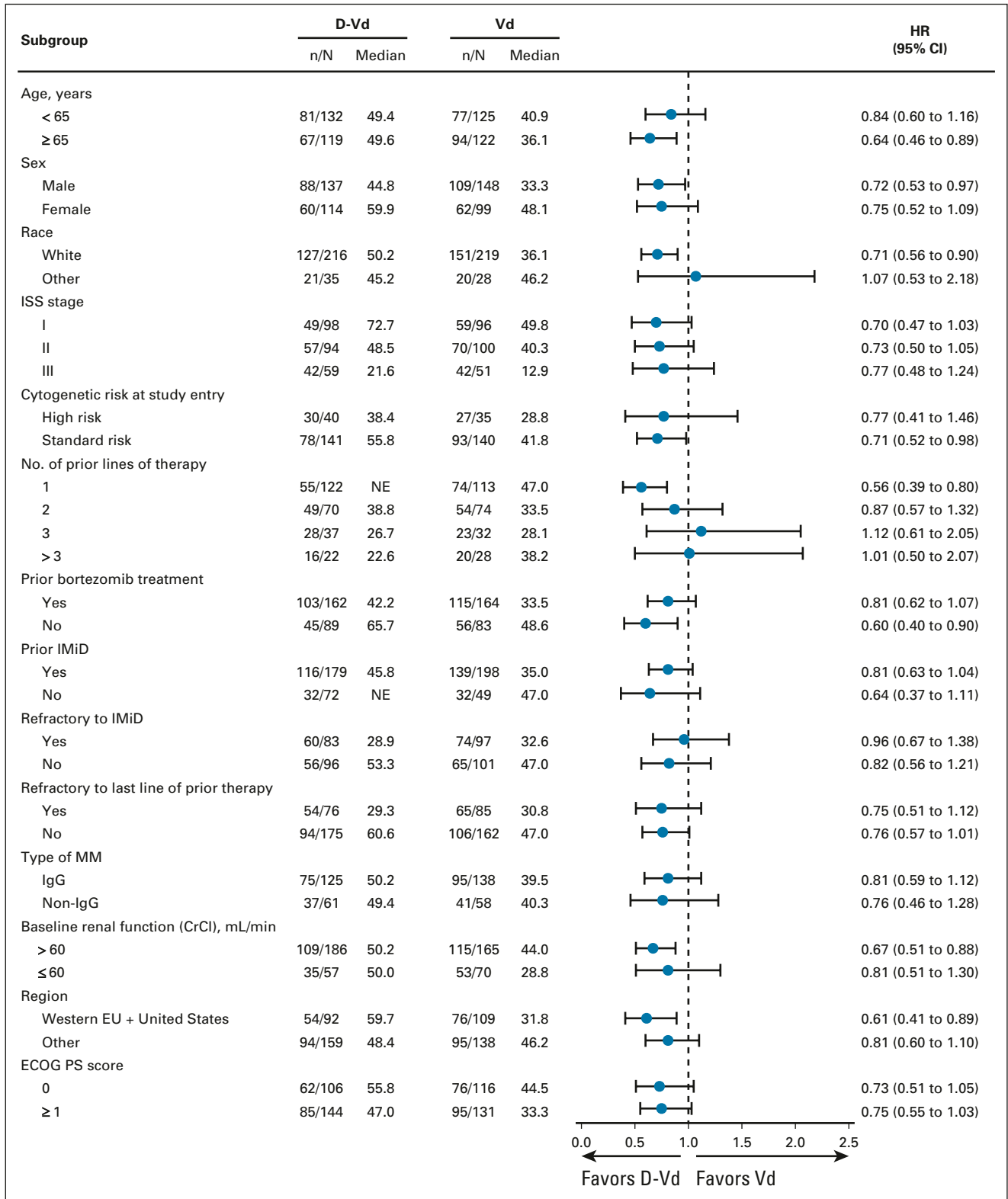


FIG 3. The results of OS in prespecified subgroups of the ITT population defined by baseline characteristics. The ISS disease stage is derived on the basis of the combination of serum β_2 -microglobulin and albumin levels. Higher stages indicate more severe disease. Cytogenetic risk was assessed locally by fluorescence in situ hybridization or karyotype testing; high risk was defined as the presence of t(4;14), t(14;16), or del17p. The subgroup analysis of the type of MM was performed on data from patients who had measurable disease in serum. CrCl, creatinine clearance; D-Vd, daratumumab, bortezomib, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; HR, hazard ratio; IgG, immunoglobulin G; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intention-to-treat; MM, multiple myeloma; NE, not estimable; OS, overall survival; Vd, bortezomib and dexamethasone.

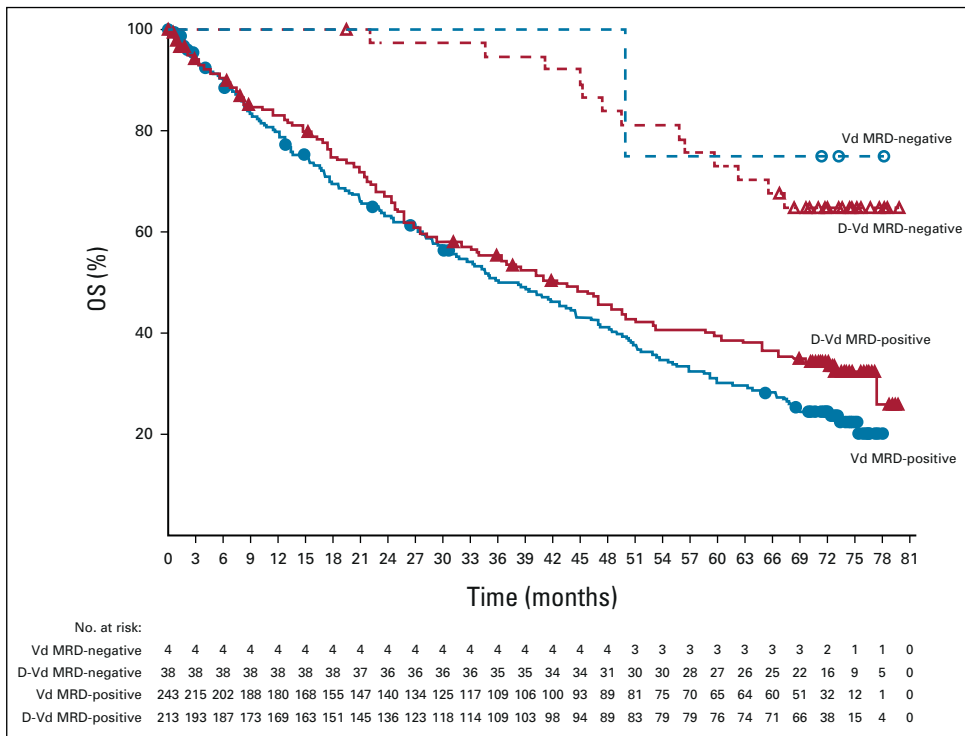


FIG 4. Kaplan–Meier estimates of OS by MRD status among patients in the ITT population. D-Vd, daratumumab, bortezomib, and dexamethasone; ITT, intention-to-treat; MRD, minimal residual disease; OS, overall survival; Vd, bortezomib and dexamethasone.

the risk of disease progression or death compared with Vd alone (median follow-up, 50.2 months).¹⁹ Median PFS was 16.7 months in the D-Vd group versus 7.1 months in the Vd group (HR, 0.31; 95% CI, 0.24 to 0.39; $P < .0001$).¹⁹

In prespecified subgroup analyses of OS, an OS advantage was observed with D-Vd compared with Vd for most subgroups, including patients age ≥ 65 years, patients who have received one or two prior lines of therapy, and patients with prior immunomodulatory drug or bortezomib treatment. It is noteworthy that OS benefit was most pronounced in patients who received one prior line of therapy (HR, 0.56; 95% CI, 0.39 to 0.80), supporting early use of daratumumab in treatment. These OS results also reinforce those from the previous updated PFS analysis (median follow-up, 50.2 months), which showed the most pronounced PFS benefit of D-Vd in patients who received one prior line of therapy, with a 79% reduction in the risk of disease progression or death versus Vd alone (median, 27.0 v 7.9 months; HR, 0.21; 95% CI, 0.15 to 0.31; $P < .0001$).¹⁹

Importantly, OS benefit was observed despite crossover in the Vd arm to daratumumab subsequent therapy. As noted earlier in the article, patients in the Vd group were offered daratumumab monotherapy after disease progression or a washout period. Approximately 63% of patients (125/200) in the Vd arm who received subsequent therapy received salvage daratumumab, primarily as monotherapy but also in combination regimens; 49 patients received first subsequent therapy with daratumumab (45 as monotherapy, four in

various combination regimens). We realize that allowing this type of crossover per study protocol may confound OS results. Patients received daratumumab monotherapy as this was the approved and reimbursed regimen available to patients at the time this study was performed.

No new safety concerns were reported after extended follow-up. Grade 3/4 infections were reported more frequently with D-Vd versus Vd, but the rate of infections leading to treatment discontinuation was low and similar between groups. Second primary malignancies were reported more commonly in the D-Vd group than in the Vd group; however, the incidence was similar between groups when adjusted for exposure to study treatment.

While cross-trial comparisons should be interpreted cautiously, the CASTOR OS data reported herein (median OS, 49.6 months) are consistent with previously reported data in RRMM (ASPIRE and ELOQUENT-2),^{23,24} despite differences in patient demographics. In the phase III ASPIRE study of patients with RRMM and one to three prior lines of therapy, at a median follow-up of 67.1 months, median OS was 48.3 months with carfilzomib-Rd versus 40.4 months with Rd alone (HR, 0.79; 95% CI, 0.67 to 0.95; 1-sided $P = .0045$).²³ Similarly, in the phase III ELOQUENT-2 study, at a minimum follow-up of 70.6 months, the combination of elotuzumab and Rd significantly improved OS versus Rd alone (median, 48.3 v 39.6 months, respectively; HR, 0.82; 95.4% CI, 0.68 to 1.00; $P = .0408$) in patients with RRMM and one to three prior lines of therapy.²⁴ On the basis of the results of these three trials, the

TABLE 1. Most Common (> 15% of Patients) and Grade 3/4 (> 5% of Patients) TEAEs in the Safety Population

TEAE	All Grades		Grade 3/4	
	D-Vd (n = 243)	Vd (n = 237)	D-Vd (n = 243)	Vd (n = 237)
Hematologic, No. (%)				
Thrombocytopenia	145 (59.7)	105 (44.3)	112 (46.1)	78 (32.9)
Anemia	73 (30.0)	75 (31.6)	39 (16.0)	38 (16.0)
Neutropenia	48 (19.8)	23 (9.7)	33 (13.6)	11 (4.6)
Lymphopenia	33 (13.6)	9 (3.8)	25 (10.3)	6 (2.5)
Nonhematologic, No. (%)				
Peripheral sensory neuropathy	122 (50.2)	90 (38.0)	11 (4.5)	16 (6.8)
Upper respiratory tract infection	90 (37.0)	43 (18.1)	6 (2.5)	1 (0.4)
Diarrhea	88 (36.2)	53 (22.4)	10 (4.1)	3 (1.3)
Cough	71 (29.2)	30 (12.7)	0 (0.0)	0 (0.0)
Fatigue	57 (23.5)	58 (24.5)	13 (5.3)	8 (3.4)
Constipation	56 (23.0)	38 (16.0)	0 (0.0)	2 (0.8)
Back pain	54 (22.2)	24 (10.1)	6 (2.5)	3 (1.3)
Arthralgia	49 (20.2)	14 (5.9)	4 (1.6)	0 (0.0)
Edema peripheral	48 (19.8)	20 (8.4)	1 (0.4)	0 (0.0)
Dyspnea	47 (19.3)	21 (8.9)	10 (4.1)	2 (0.8)
Pyrexia	46 (18.9)	28 (11.8)	5 (2.1)	3 (1.3)
Insomnia	44 (18.1)	36 (15.2)	2 (0.8)	3 (1.3)
Pneumonia	40 (16.5)	32 (13.5)	26 (10.7)	24 (10.1)
Bronchitis	38 (15.6)	15 (6.3)	7 (2.9)	3 (1.3)
Nausea	37 (15.2)	27 (11.4)	2 (0.8)	0 (0.0)
Hypertension	30 (12.3)	8 (3.4)	18 (7.4)	2 (0.8)
Asthenia	27 (11.1)	37 (15.6)	2 (0.8)	5 (2.1)

Abbreviations: D-Vd, daratumumab, bortezomib, and dexamethasone; TEAE, treatment-emergent adverse event; Vd, bortezomib and dexamethasone.

benchmark for survival in RRMM is approximately 4 years. It is also noteworthy that the median OS in the Vd arm of CASTOR (38.5 months) was consistent with that observed in the Vd arm of the phase III ENDEAVOR study (38.8 months).²⁵

Similar to CASTOR, the results from the phase III POLLUX study also support utilizing a daratumumab-containing regimen after first relapse in patients with RRMM who are not refractory to lenalidomide.^{13,26,27} Moreover, the results from the phase III ALCYONE and MAIA trials demonstrate that adding daratumumab to standard-of-care regimens significantly improves OS and PFS compared with standard of care alone in patients with transplant-ineligible NDMM.^{10,22} Real-world data from a patient chart review in Europe reported high attrition rates that increased with each subsequent line of therapy, with 95% of patients receiving first-line therapy and only 61% and 38% receiving second-line and third-line therapy, respectively.²⁸ In a retrospective analysis of 3 US databases, attrition rates were high after first (57%) and each subsequent line of therapy (43%-46%) in nontransplant elderly patients with NDMM.²⁹ Taken together, these real-world data, in conjunction with the prolonged OS observed with daratumumab-containing regimens in both the NDMM

(ALCYONE and MAIA) and now RRMM (CASTOR and POLLUX) treatment settings, support early use of daratumumab to induce deep and sustained responses and prolonged disease control to potentially delay clonal evolution and subsequent drug resistance.³⁰ As use of daratumumab increases in the frontline treatment setting, the role of retreatment with daratumumab after progression will be of growing interest. Retrospective analyses suggest clinical efficacy with daratumumab retreatment,^{31,32} but the results of ongoing (LYNX; ClinicalTrials.gov identifier: [NCT03871829](https://clinicaltrials.gov/ct2/show/study/NCT03871829)) and future studies will further define the potential role of daratumumab retreatment after progression.

In conclusion, to our knowledge, these results, combined with the OS results reported with D-Rd in the phase III POLLUX study,²⁷ demonstrate for the first time an OS benefit with daratumumab-containing regimens in patients with RRMM. Treatment of patients with RRMM with D-Vd results in a significant reduction in the risk of death compared with Vd alone, with the greatest OS benefit observed in patients who received one prior line of therapy. These results provide strong rationale for early use of daratumumab to maximize patient benefit.

AFFILIATIONS

- ¹Erasmus MC Cancer Institute, Rotterdam, the Netherlands
²Mayo Clinic Florida, Jacksonville, FL
³Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center of Hamburg-Eppendorf, Hamburg, Germany
⁴Winship Cancer Institute, Emory University, Atlanta, GA
⁵Department of Internal Medicine and Haematology, Semmelweis University, Budapest, Hungary
⁶Ankara University, Ankara, Turkey
⁷1st Department of Medicine – Department of Hematology, First Faculty of Medicine, Charles University and General Hospital in Prague, Prague, Czech Republic
⁸Clínica Médica São Germano, São Paulo, Brazil
⁹Third Department of Medicine, University Medical Center of the Johannes Gutenberg University, Mainz, Germany
¹⁰University Hospital of Salamanca/IBSAL/Cancer Research Center-IBMCC (USAL-CSIC), Salamanca, Spain
¹¹Department of Medicine, University of Colorado, Aurora, CO
¹²Albert Schweitzer Hospital, Dordrecht, the Netherlands
¹³Genmab US Inc, Plainsboro, NJ
¹⁴Janssen Research & Development, LLC, Spring House, PA
¹⁵Janssen Research & Development, LLC, Raritan, NJ
¹⁶Janssen Research & Development, LLC, Beijing, China
¹⁷Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne, Australia

CORRESPONDING AUTHOR

Pieter Sonneveld, MD, PhD, Erasmus MC Cancer Institute, PO Box 2040, 3000 CA Rotterdam, the Netherlands; e-mail: p.sonneveld@erasmusmc.nl.

SUPPORT

Supported by Janssen Research & Development, LLC.

CLINICAL TRIAL INFORMATION

NCT02136134 [CASTOR]

REFERENCES

- de Weers M, Tai YT, van der Veer MS, et al: Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* 186:1840-1848, 2011
- Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al: Direct *in vitro* comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. *Blood* 124:3474, 2014
- Overdijk MB, Verploegen S, Bögels M, et al: Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs* 7:311-321, 2015
- Overdijk MB, Jansen JH, Nederend M, et al: The therapeutic CD38 monoclonal antibody daratumumab induces programmed cell death via Fcγ receptor-mediated cross-linking. *J Immunol* 197:807-813, 2016
- Krejci J, Casneuf T, Nijhof IS, et al: Daratumumab depletes CD38⁺ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood* 128:384-394, 2016
- Adams HC III, Stevens F, Krejci J, et al: High-parameter mass cytometry evaluation of relapsed/refractory multiple myeloma patients treated with daratumumab demonstrates immune modulation as a novel mechanism of action. *Cytometry A* 95:279-289, 2019
- Casneuf T, Adams HC III, van de Donk NWCJ, et al: Deep immune profiling of patients treated with lenalidomide and dexamethasone with or without daratumumab. *Leukemia* 35:573-584, 2021
- Kinder M, Bahlis NJ, Malavasi F, et al: Comparison of CD38 antibodies *in vitro* and *ex vivo* mechanisms of action in multiple myeloma. *Haematologica* 106:2004-2008, 2021
- Moreau P, Attal M, Hulin C, et al: Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): A randomised, open-label, phase 3 study. *Lancet* 394:29-38, 2019
- Mateos MV, Cavo M, Blade J, et al: Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): A randomised, open-label, phase 3 trial. *Lancet* 395:132-141, 2020
- Facon T, Kumar S, Plesner T, et al: Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med* 380:2104-2115, 2019
- Mateos MV, Sonneveld P, Hungria V, et al: Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in patients with previously treated multiple myeloma: Three-year follow-up of CASTOR. *Clin Lymphoma Myeloma Leuk* 20:509-518, 2020

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.21.02734>.

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>.

AUTHOR CONTRIBUTIONS

Conception and design: Asher Chanan-Khan, Katja Weisel, Tahamtan Ahmadi, Robin Carson
Provision of study materials or patients: Asher Chanan-Khan, Katja Weisel, Tamas Masszi, Meral Beksac, Vania Hungria, Markus Munder, Maria-Victoria Mateos
Collection and assembly of data: Katja Weisel, Tamas Masszi, Meral Beksac, Ivan Spicka, Vania Hungria, Maria-Victoria Mateos, Tomer M. Mark, Tahamtan Ahmadi, Wendy Garvin Mayo, Robin Carson, Andrew Spencer
Data analysis and interpretation: Pieter Sonneveld, Asher Chanan-Khan, Katja Weisel, Ajay K. Nooka, Meral Beksac, Ivan Spicka, Vania Hungria, Markus Munder, Maria-Victoria Mateos, Tomer M. Mark, Mark-David Levin, Tahamtan Ahmadi, Xiang Qin, Xue Gai, Jodi Carey, Robin Carson, Andrew Spencer
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank the patients who participated in the CASTOR study and their families, as well as the study coinvestigators, research nurses, and coordinators at each of the clinical sites. Medical writing and editorial support were provided by Lisa Shannon, PharmD, of Lumanity Communications Inc, and were funded by Janssen Global Services, LLC.

13. Bahlis NJ, Dimopoulos MA, White DJ, et al: Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia* 34:1875-1884, 2020
14. Dimopoulos MA, Terpos E, Boccadoro M, et al: Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): An open-label, randomised, phase 3 trial. *Lancet Oncol* 22:801-812, 2021
15. DARZALEX® (daratumumab) [package insert]. Horsham, PA, Janssen Biotech, Inc, 2022
16. European Medicines Agency: DARZALEX 20 mg/mL concentrate for solution for infusion [summary of product characteristics]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf
17. Palumbo A, Chanan-Khan A, Weisel K, et al: Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 375:754-766, 2016
18. Spencer A, Lentzsch S, Weisel K, et al: Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: Updated analysis of CASTOR. *Haematologica* 103:2079-2087, 2018
19. Weisel KC, Sonneveld P, Mateos MV, et al: Efficacy and safety of daratumumab, bortezomib, and dexamethasone (D-Vd) versus bortezomib and dexamethasone (Vd) in first relapse patients (pts) with multiple myeloma (MM): Four-year update of CASTOR. Poster presented at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition, Orlando, FL, December 7-10, 2019
20. Durie BGM, Harousseau JL, Miguel JS, et al: International uniform response criteria for multiple myeloma. *Leukemia* 20:1467-1473, 2006
21. Rajkumar SV, Harousseau JL, Durie B, et al: Consensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. *Blood* 117:4691-4695, 2011
22. Facon T, Kumar SK, Plesner T, et al: Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): Overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 22:1582-1596, 2021
23. Siegel DS, Dimopoulos MA, Ludwig H, et al: Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol* 36:728-734, 2018
24. Dimopoulos MA, Lonial S, White D, et al: Elotuzumab, lenalidomide, and dexamethasone in RRMM: Final overall survival results from the phase 3 randomized ELOQUENT-2 study. *Blood Cancer J* 10:91, 2020
25. Orłowski RZ, Moreau P, Niesvizky R, et al: Carfilzomib-dexamethasone versus bortezomib-dexamethasone in relapsed or refractory multiple myeloma: Updated overall survival, safety, and subgroups. *Clin Lymphoma Myeloma Leuk* 19:522-530.e1, 2019
26. Dimopoulos MA, Oriol A, Nahi H, et al: Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 375:1319-1331, 2016
27. Dimopoulos MA, Oriol A, Nahi H, et al: Overall survival with daratumumab, lenalidomide, and dexamethasone in previously treated multiple myeloma (POLLUX): A randomized, open-label, phase III trial. *J Clin Oncol* 41:1590-1599, 2023
28. Yong K, Delforge M, Driessen C, et al: Multiple myeloma: Patient outcomes in real-world practice. *Br J Haematol* 175:252-264, 2016
29. Fonseca R, Usmani SZ, Mehra M, et al: Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. *BMC Cancer* 20:1087, 2020
30. Suzuki K, Nishiwaki K, Yano S: Treatment strategies considering micro-environment and clonal evolution in multiple myeloma. *Cancers (Basel)* 13:215, 2021
31. Nooka AK, Joseph NS, Kaufman JL, et al: Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: Utility of re-treatment with daratumumab among refractory patients. *Cancer* 125:2991-3000, 2019
32. Hussain MJ, Robinson MM, Hamadeh I, et al: Daratumumab, pomalidomide and dexamethasone combination therapy in daratumumab and/or pomalidomide refractory multiple myeloma. *Br J Haematol* 186:140-144, 2019



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Overall Survival With Daratumumab, Bortezomib, and Dexamethasone in Previously Treated Multiple Myeloma (CASTOR): A Randomized, Open-Label, Phase III Trial**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

Pieter Sonneveld

Consulting or Advisory Role: Celgene, Janssen, Amgen, Karyopharm Therapeutics, CARsgen Therapeutics

Research Funding: Janssen (Inst), Amgen (Inst), SkylineDx (Inst), Bristol Myers Squibb/Celgene (Inst)

Asher Chanan-Khan

Leadership: Starton Therapeutics, Cellectar

Stock and Other Ownership Interests: Matthew & Asher Inc, NanoDev Therapeutics, Starton Therapeutics, Cellectar

Honoraria: BeiGene, Ascentage Pharma

Research Funding: Ascentage Pharma

Patents, Royalties, Other Intellectual Property: Patent on PSMB9 biomarker

Katja Weisel

Honoraria: Amgen, Bristol Myers Squibb/Celgene, Janssen-Cilag, GlaxoSmithKline (Inst), Adaptive Biotechnologies, Karyopharm Therapeutics, Takeda, Sanofi, AbbVie, GlaxoSmithKline, Novartis, Pfizer, Celgene, Oncoceptides, Roche

Consulting or Advisory Role: Amgen, Adaptive Biotechnologies, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen-Cilag, Karyopharm Therapeutics, Sanofi, Takeda, Oncoceptides, Roche

Research Funding: Amgen (Inst), Celgene (Inst), Sanofi (Inst), Janssen-Cilag (Inst), Bristol Myers Squibb/Celgene (Inst), GlaxoSmithKline (Inst)

Travel, Accommodations, Expenses: Amgen, Celgene, Bristol Myers Squibb/Celgene, Janssen-Cilag, GlaxoSmithKline, Takeda

Ajay K. Nooka

Honoraria: Amgen, Janssen Oncology, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Takeda, Oncoceptides, Karyopharm Therapeutics, Adaptive Biotechnologies, Genzyme, BeyondSpring Pharmaceuticals, Secura Bio

Consulting or Advisory Role: Amgen, Janssen Oncology, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Takeda, Oncoceptides, Karyopharm Therapeutics, Adaptive Biotechnologies, Genzyme, BeyondSpring Pharmaceuticals, Secura Bio

Research Funding: Amgen (Inst), Janssen Oncology (Inst), Takeda (Inst), Bristol Myers Squibb/Celgene (Inst), Arch Oncology (Inst), GlaxoSmithKline (Inst)

Travel, Accommodations, Expenses: GlaxoSmithKline

Tamas Masszi

Consulting or Advisory Role: AbbVie, Bristol Myers Squibb/Celgene, Janssen-Cilag, Novartis, Pfizer, Takeda

Meral Beksac

Consulting or Advisory Role: Janssen Oncology (Inst), Bristol Myers Squibb/Celgene Turkey (Inst), Amgen (Inst), Takeda (Inst), Oncoceptides (Inst), Sanofi (Inst)

Speakers' Bureau: Amgen (Inst), Sanofi (Inst)

Ivan Spicka

Honoraria: Amgen, Janssen-Cilag, Takeda, Novartis

Consulting or Advisory Role: Celgene, Amgen, Janssen-Cilag, Takeda, Novartis, Sanofi

Speakers' Bureau: Celgene, Amgen, Janssen-Cilag, Takeda, Bristol Myers Squibb/Celgene, Novartis, Sanofi

Travel, Accommodations, Expenses: Celgene, Amgen, Janssen-Cilag, Bristol Myers Squibb/Celgene

Vania Hungria

Consulting or Advisory Role: AbbVie, Janssen-Cilag, Takeda, Sanofi, Bristol Myers Squibb/Celgene Brazil, Amgen, Pfizer

Speakers' Bureau: Janssen-Cilag, Takeda, Bristol Myers Squibb/Celgene Brazil, Sanofi, Amgen, GlaxoSmithKline

Markus Munder

Honoraria: Janssen Oncology, Bristol Myers Squibb/Celgene GmbH & Co KG, GlaxoSmithKline, Sanofi, Abbvie

Consulting or Advisory Role: Janssen Oncology, Bristol Myers Squibb/Celgene GmbH & Co KG, GlaxoSmithKline, Sanofi, Takeda, Amgen

Maria-Victoria Mateos

Honoraria: Janssen-Cilag, Celgene, Amgen, Takeda, GlaxoSmithKline, AbbVie/Genentech, Sanofi

Consulting or Advisory Role: Takeda, Janssen-Cilag, Celgene, Amgen, AbbVie, GlaxoSmithKline, Pfizer, Regeneron, Roche/Genentech

Tomer M. Mark

Employment: Karyopharm Therapeutics

Stock and Other Ownership Interests: Karyopharm Therapeutics, Adaptive Biotechnologies, AbbVie

Consulting or Advisory Role: Adaptive Biotechnologies, Genzyme, Bristol Myers Squibb/Celgene, Amgen, Sanofi, Takeda

Research Funding: Bristol Myers Squibb/Celgene (Inst), Janssen (Inst)

Mark-David Levin

Honoraria: AbbVie, Celgene, Janssen, Takeda

Travel, Accommodations, Expenses: Takeda, Janssen, AbbVie

Tahamtan Ahmadi

Employment: Genmab

Leadership: Genmab

Stock and Other Ownership Interests: Genmab

Xiang Qin

Employment: Janssen Research & Development

Wendy Garvin Mayo

Employment: Janssen Research & Development

Xue Gai

Employment: Janssen Research & Development

Stock and Other Ownership Interests: Janssen Research & Development

Travel, Accommodations, Expenses: Janssen Research & Development

Jodi Carey

Employment: Janssen Research & Development

Stock and Other Ownership Interests: Johnson & Johnson

Robin Carson

Employment: Johnson & Johnson

Stock and Other Ownership Interests: Johnson & Johnson

Andrew Spencer

Honoraria: Janssen-Cilag, Bristol Myers Squibb/Celgene

Consulting or Advisory Role: Janssen-Cilag, Bristol Myers Squibb/Celgene

Speakers' Bureau: Janssen-Cilag

Research Funding: Janssen-Cilag

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Baseline Demographic and Clinical Characteristics¹⁷

Characteristic	D-Vd (n = 251)	Vd (n = 247)
Age, years		
Median (range)	64 (30-88)	64 (33-85)
≥ 75, No. (%)	23 (9)	35 (14)
ISS stage, No. (%) ^a		
I	98 (39)	96 (39)
II	94 (37)	100 (40)
III	59 (24)	51 (21)
Median (range) time from diagnosis, years	3.87 (0.7-20.7)	3.72 (0.6-18.6)
Prior lines of therapy, No. (%)		
Median (range)	2 (1-9)	2 (1-10)
1	122 (49)	113 (46)
2	70 (28)	74 (30)
3	37 (15)	32 (13)
> 3	22 (9)	28 (11)
Prior PI, No. (%)	169 (67)	172 (70)
Prior bortezomib	162 (65)	164 (66)
Prior IMiD, No. (%)	179 (71)	198 (80)
Prior thalidomide	125 (50)	121 (49)
Prior lenalidomide	89 (35)	120 (49)
Prior PI + IMiD, No. (%)	112 (45)	129 (52)
Refractory to lenalidomide, No. (%)	60 (24)	81 (33)
Cytogenetic risk profile, n/N (%) ^b		
Standard risk	140/181 (77)	137/174 (79)
High risk	41/181 (23)	37/174 (21)

Abbreviations: D-Vd, daratumumab, bortezomib, and dexamethasone; IMiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor; Vd, bortezomib and dexamethasone.

^aISS stage was based on the combination of serum β_2 -microglobulin and albumin levels.

^bCytogenetic risk was assessed locally by fluorescence in situ hybridization or karyotype testing; high risk was defined as the presence of t(4;14), t(14;16), or del17p.

TABLE A2. Most Common First Line of Subsequent Therapy in the ITT Population

Subsequent Therapy	D-Vd (n = 251)	Vd (n = 247)
Patients receiving subsequent therapy, No. (%)	163 (64.9)	201 (81.4)
Most common first line of subsequent therapy, No. (%)		
Lenalidomide/dexamethasone	39 (23.9)	38 (18.9)
Pomalidomide/dexamethasone	12 (7.4)	22 (10.9)
Autologous stem-cell transplant	11 (6.7)	1 (0.5)
Carfilzomib/lenalidomide/dexamethasone	9 (5.5)	5 (2.5)
Carfilzomib/dexamethasone	8 (4.9)	12 (6.0)
Bortezomib/dexamethasone	7 (4.3)	11 (5.5)
Cyclophosphamide/dexamethasone	7 (4.3)	11 (5.5)
Lenalidomide/cyclophosphamide/dexamethasone	6 (3.7)	7 (3.5)
Thalidomide/cyclophosphamide/dexamethasone	6 (3.7)	5 (2.5)
Bendamustine	6 (3.7)	4 (2.0)
Lenalidomide/dexamethasone/ixazomib	6 (3.7)	2 (1.0)
Bendamustine/bortezomib/dexamethasone	3 (1.8)	3 (1.5)
Bortezomib/cyclophosphamide/dexamethasone	3 (1.8)	2 (1.0)
Lenalidomide/dexamethasone/elotuzumab	3 (1.8)	0 (0.0)
Bortezomib/dexamethasone/panobinostat	1 (0.6)	3 (1.5)
Daratumumab monotherapy	0 (0.0)	45 (22.4)
Melphalan/prednisone	0 (0.0)	4 (2.0)

NOTE. First line of subsequent therapy received by ≥ 3 patients is shown.

Abbreviations: D-Vd, daratumumab, bortezomib, and dexamethasone; ITT, intention-to-treat; Vd, bortezomib and dexamethasone.