EUROPEAN HEMATOLOGY ASSOCIATION
haematologica
Journal of the European Hematology Association

Daratumumab plus bortezomib and dexamethasone *versus* bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR

by Andrew Spencer, Suzanne Lentzsch, Katja Weisel, Hervé Avet-Loiseau, Tomer M. Mark, Ivan Spicka, Tamas Masszi, Birgitta Lauri, Mark-David Levin, Alberto Bosi, Vania Hungria, Michele Cavo, Je-Jung Lee, Ajay K. Nooka, Hang Quach, Cindy Lee, Wolney Barreto, Paolo Corradini, Chang-Ki Min, Emma C. Scott, Asher A. Chanan-Khan, Noemi Horvath, Marcelo Capra, Meral Beksac, Roberto Ovilla, Jae-Cheol Jo, Ho-Jin Shin, Pieter Sonneveld, David Soong, Tineke Casneuf, Christopher Chiu, Himal Amin, Ming Qi, Piruntha Thiyagarajah, A. Kate Sasser, Jordan M. Schecter, and Maria-Victoria Mateos

Haematologica 2018 [Epub ahead of print]

Citation: Andrew Spencer, Suzanne Lentzsch, Katja Weisel, Hervé Avet-Loiseau, Tomer M. Mark, Ivan Spicka, Tamas Masszi, Birgitta Lauri, Mark-David Levin, Alberto Bosi, Vania Hungria, Michele Cavo, Je-Jung Lee, Ajay K. Nooka, Hang Quach, Cindy Lee, Wolney Barreto, Paolo Corradini, Chang-Ki Min, Emma C. Scott, Asher A. Chanan-Khan, Noemi Horvath, Marcelo Capra, Meral Beksac, Roberto Ovilla, Jae-Cheol Jo, Ho-Jin Shin, Pieter Sonneveld, David Soong, Tineke Casneuf, Christopher Chiu, Himal Amin, Ming Qi, Piruntha Thiyagarajah, A. Kate Sasser, Jordan M. Schecter, and Maria-Victoria Mateos. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018; 103:xxx
doi:10.3324/haematol.2018.194118

Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR

Authors: Andrew Spencer,[1] Suzanne Lentzsch,[2] Katja Weisel,[3] Hervé Avet-Loiseau,[4] Tomer M. Mark,[5] Ivan Spicka,[6] Tamas Masszi,[7] Birgitta Lauri,[8] Mark-David Levin,[9] Alberto Bosi,[10] Vania Hungria,[11] Michele Cavo,[12] Je-Jung Lee,[13] Ajay K. Nooka,[14] Hang Quach,[15] Cindy Lee,[16] Wolney Barreto,[17] Paolo Corradini,[18] Chang-Ki Min,[19] Emma C. Scott,[20] Asher A. Chanan-Khan,[21] Noemi Horvath,[16] Marcelo Capra,[22] Meral Beksac,[23] Roberto Ovilla,[24] Jae-Cheol Jo,[25] Ho-Jin Shin,[26] Pieter Sonneveld,[27] David Soong,[28] Tineke Casneuf,[29] Christopher Chiu,[28] Himal Amin,[30] Ming Qi,[28] Piruntha Thiyagarajah,[31] A. Kate Sasser,[32] Jordan M. Schecter,[30] and Maria-Victoria Mateos[33]

Affiliations:

[1]Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne, Australia;

[2]Division of Hematology/Oncology, Columbia University, New York, NY, USA;

[3]Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Abteilung fuer Innere Medizin II, Tuebingen, Germany;

[4]Unite de Genomique du Myelome, CHU Rangueil, Toulouse, France;

[5]Department of Medicine, University of Colorado, Aurora, CO, USA;

[6]Clinical Department of Haematology, 1st Medical Department, Charles University in Prague, Czech Republic;

[7]Department of Haematology and Stem Cell Transplantation, St László Hospital, 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary;

[8]Department of Hematology, Sunderbyn Hospital, Luleå, Sweden;

[9]Albert Schweitzer Hospital Department of Internal Medicine, Dordrecht, Netherlands;

[10]Department of Hematology, Careggi Hospital and University of Florence, Firenze, Italy;

[11]Irmandade Da Santa Casa De Misericordia De São Paulo, São Paulo, Brazil;

[12]"Seràgnoli" Institute of Hematology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy;

[13]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, South Korea;

[14]Winship Cancer Institute, Emory University, Atlanta, GA, USA;

[15]St. Vincent's Hospital, University of Melbourne, Melbourne, Australia;

[16]Royal Adelaide Hospital, North Terrace, Adelaide, Australia;

[17]Hospital Santa Marcelina, Sao Paulo, Brazil;

[18]Fondazione IRCCS Instituto Nazionale dei Tumori, University of Milan, Milan, Italy;

[19]Seoul St. Mary's Hospital, Seoul, Korea;

[20]Oregon Health & Science University, Portland, OR, USA;

[21]Mayo Clinic Florida, Jacksonville, FL, USA;

[22]Instituto do Cancer-Hospital Mae de Deus, Porto Alegre, Brazil;

[23]Ankara University, Ankara, Turkey;

[24]Hospital Angeles Lomas, Naucalpan de Juárez y alrededores, México;

[25]Ulsan University Hospital, Ulsan, South Korea;

[26]Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Medical Research Institute, Pusan National University Hospital, Busan, South Korea;

[27]Erasmus Medical Center, Rotterdam, The Netherlands;

[28]Janssen Research and Development, LLC, Spring House, PA, USA;

[29]Janssen Research & Development, Beerse, Belgium;

[30]Janssen Research and Development, LLC, Raritan, NJ, USA;

[31]Janssen Research & Development, High Wycombe, UK;

[32]Genmab US, Inc, Princeton, NJ, USA;

[33]University Hospital of Salamanca/IBSAL, Salamanca, Spain.

Running Head: Subgroup Analyses of CASTOR

Research Support: This study was funded by Janssen Research & Development, LLC.

Results of this analysis were presented, in part, at the American Society of Clinical Oncology (ASCO) Annual Meeting, June 2-6, 2017, Chicago, IL, USA, and at the 22nd Congress of the European Hematology Association (EHA), June 22-25, 2017, Madrid, Spain.

Correspondence to: Andrew Spencer, MD

Malignant Haematology and Stem Cell Transplantation Service

Alfred Health-Monash University

Wellington Rd, Clayton VIC 3800

Melbourne, Australia

Telephone: +61 3 9076 3392

Email: aspencer@netspace.net.au

Disclaimers:

Declaration of interests

AS received research funding and personal fees from Janssen Cilag. SL holds stock and/or stock options at Caelum Biosciences; consulted for Bristol-Myers Squibb, Celgene, and Janssen; and served on a speakers bureau for Axiom (Takeda). KW received honoraria from and consulted for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Takeda, and Onyx; received research funding from Janssen, Celgene, Amgen, and Sanofi; and received travel expenses from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, and Takeda. 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. IS served as a consultant for Bristol-Myers Squibb, Celgene, Amgen, and Janssen Cilag; received research funding from Celgene; received honoraria from Bristol-Myers Squibb, Celgene, Amgen, Janssen Cilag, and Millennium; and was a member of the advisory committee for Bristol-Myers Squibb, Celgene, and Janssen Cilag. M-DL received honoraria from Janssen, Sandoz, Roche, AbbVie, Celgene, and Amgen. VH served as a consultant or advisor for Amgen, Celgene, Janssen, and Takeda. M Cavo received honoraria from Bristol-Myers Squibb, Celgene, Amgen, Janssen, and Takeda. J-JL is an employee of Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, South Korea. AKN consulted for Amgen, Novartis, and Spectrum. HQ received honoraria from and consulted for Amgen, Janssen-Cilag, Takeda, and Celgene and received research funding from Amgen and Celgene. CL received honoraria from and consulted for Amgen, Janssen-Cilag, Takeda, and Celgene. PC consulted for Takeda and received honoraria from Celgene, Janssen,

Novartis, Roche, Takeda, Sanofi, Servier, and Gilead. ECS received research funding from Takeda and Amgen and has served on advisory boards for Novartis, Incyte, Takeda, and Amgen. AAC-K received research funding from the Mayo Clinic. NH served on the board of directors or advisory committees for Janssen. M Capra served on a speakers bureau for Janssen. MB received honoraria from and participated in advisory boards for Celgene, BMS, Amgen, Novartis, Janssen-Cilag, and Takeda. RO consulted for Janssen. PS received research funding from Janssen, Celgene, Amgen, Karyopharm, SkylineDx, Takeda, and Novartis and received personal fees from Janssen, Celgene, and Amgen. DS, TC, CC, HA, MQ, PT, and JMS are employees of Janssen. TC, AKS, MQ, and JMS hold equity in Johnson & Johnson. AKS is a former employee of Janssen and is a current employee of Genmab. M-VM received honoraria from and consulted for Janssen, Celgene, Takeda, and Amgen. TMM, TM, BL, AB, WB, C-KM, J-CJ, and H-JS declare no conflicts of interest.

Trial registration: clinicaltrials.gov identifier: NCT02136134.

ABSTRACT

Daratumumab, a CD38 human monoclonal antibody, demonstrated significant clinical activity in combination with bortezomib and dexamethasone versus bortezomib and dexamethasone alone in the primary analysis of CASTOR, a phase 3 study in relapsed and/or refractory multiple myeloma. A post hoc analysis based on treatment history and longer follow-up is presented. After 19.4 (range: 0 to 27.7) months of median follow-up, daratumumab plus bortezomib and dexamethasone prolonged progression-free survival (median: 16.7 versus 7.1 months; hazard ratio, 0.31; 95% confidence interval, 0.24-0.39; *P* <0.0001) and improved the overall response rate (83.8% versus 63.2%; *P* <0.0001) compared with bortezomib and dexamethasone alone. The progression-free survival benefit of daratumumab plus bortezomib and dexamethasone was most apparent in patients with 1 prior line of therapy (median: not reached versus 7.9 months; hazard ratio, 0.19; 95% confidence interval, 0.12-0.29; *P* <0.0001). Daratumumab plus bortezomib and dexamethasone was also superior to bortezomib and dexamethasone alone in subgroups based on prior treatment exposure (bortezomib, thalidomide, or lenalidomide), lenalidomide-refractory status, time since last therapy (≤12, >12, ≤6, or >6 months), or cytogenetic risk. Minimal residual disease-negative rates were >2.5-fold higher with daratumumab across subgroups. The safety profile of daratumumab plus bortezomib and dexamethasone remained consistent with longer follow-up. Daratumumab plus bortezomib and dexamethasone demonstrated significant clinical activity across clinically relevant subgroups and provided the greatest benefit to patients treated at first relapse.

Trial registration: clinicaltrials.gov identifier: NCT02136134.

INTRODUCTION

As multiple myeloma (MM) progresses, a reduction in the duration and depth of response is observed with each treatment relapse, as a result of diminished sensitivity of heavily treated patients to subsequent therapies.[1]

Proteasome inhibitors (PI) are widely used due to their clinical effectiveness, manageable safety profile, and combinability with other therapies.[2] However, in several studies of novel PI-based regimens in relapsed and/or refractory MM (RRMM), deep clinical responses were uncommon.[3-6] PI-based regimens that generate deeper responses in RRMM are an unmet need.

Daratumumab, a human IgGκ monoclonal antibody targeting CD38, has a direct on-tumor and immunomodulatory mechanism of action.[7-12] In combination with standard of care regimens, (bortezomib and dexamethasone [Vd; CASTOR] or lenalidomide and dexamethasone [Rd; POLLUX]), daratumumab induced rapid, deep, and durable responses, reducing the risk of disease progression or death by >60%, versus Vd or Rd in relapsed patients.[13,14] Based on the superior progression-free survival (PFS) benefit, daratumumab-Vd (D-Vd) and daratumumab-Rd (D-Rd) were approved in the United States and Europe for MM patients who have received ≥1 prior therapy.[15,16] In addition, daratumumab plus pomalidomide and dexamethasone was approved in the United States for MM patients after 2 prior therapies including lenalidomide and a PI.[15] More recently, daratumumab in combination with bortezomib, melphalan, and prednisone was approved in the United States for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.[15]

At the time of the event-driven, pre-specified primary analysis (median follow-up: 7.4 months) of the CASTOR study, PFS was significantly prolonged with D-Vd versus Vd (median: not reached versus 7.2 months; hazard ratio [HR]: 0.39; 95% confidence interval [CI], 0.28-0.53; *P* <0.0001).[13] This updated analysis provides an additional 12 months of follow-up for efficacy and safety compared with the primary analysis, including updated PFS in the intent-to-treat population, and presents an exploratory *post hoc* analysis of CASTOR to identify patient subgroups that may benefit most from D-Vd.

METHODS

Study Design

CASTOR (ClinicalTrials.gov Identifier: NCT02136134) is an ongoing multi-center, open-label, randomized, active-controlled, phase 3 study of D-Vd versus Vd in patients with RRMM who received ≥1 prior line of therapy. The study design and primary results were previously published.[13] Briefly, patients were randomized 1:1 to D-Vd or Vd. Randomization was balanced and stratified by International Staging System (I, II, or III) at screening (central laboratory results), number of prior lines of therapy (1 versus 2 or 3 versus >3), and prior bortezomib exposure (no versus yes). The study protocol was approved by an independent ethics committee or institutional review board at each study center, and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Patients

Eligible patients had ≥1 prior line of therapy, achieved at least a partial response to ≥1 prior MM treatment, and had progressive disease per International Myeloma Working Group [IMWG] criteria[17,18] on or after their last regimen. Patients refractory to bortezomib or another PI (ixazomib or carfilzomib following a protocol amendment) were ineligible.

Procedures

Patients received 8 cycles of bortezomib (1.3 mg/m^2 subcutaneously on Days 1, 4, 8, 11) and dexamethasone (20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, 12) with or without daratumumab (16 mg/kg intravenously once weekly in Cycles 1-3, Day 1 of Cycles 4-8, then every 4 weeks until disease progression, unacceptable toxicity, or withdrawal of consent). Cycle durations were 21 days for Cycles 1 to 8 and 28 days for Cycle 9 onwards. A protocol amendment after the primary analysis allowed patients who progressed on Vd to receive daratumumab monotherapy.

Assessments and Endpoints

The primary endpoint was PFS; secondary endpoints included time to disease progression, overall response rate (ORR), minimal residual disease (MRD), and safety. This exploratory, post hoc, secondary analysis examined subpopulations according to prior lines of therapy (1, 2 to 3, >3, or 1 to 3), prior treatment exposure (bortezomib, thalidomide, or lenalidomide), refractoriness to lenalidomide at the last prior line of therapy, time since last therapy (≤12, >12, ≤6, or >6 months), and cytogenetic risk assessed centrally by next generation sequencing.[19] Site investigators determined numbers of prior lines of therapy using IMWG guidelines.[18] Time since last therapy was the duration between the end date of the last line of prior therapy and randomization date. PFS, ORR, and MRD-negativity at 10^{-5} and 10^{-6} sensitivity thresholds were

assessed for each subgroup. PFS based on MRD (10^{-5}) and cytogenetic risk status was also examined. Health-related quality of life (HRQoL) was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-C30) and the EuroQol 5 Dimensions Questionnaire (EQ-5D-5L) tools.

The supplementary appendix provides full details of statistical analyses and MRD, cytogenetic, and HRQoL assessments.

RESULTS

Of 498 patients, 251 and 247 were randomized to D-Vd and Vd, respectively [**Figure S1]**. Patient demographics and baseline clinical characteristics were previously published and are well-balanced between groups.[13] Relevant clinical characteristics, including treatment history and cytogenetic-risk status, were balanced between groups and are summarized in **Table 1** and **Table S1**. Briefly, patients in CASTOR received a median of 2 prior lines of therapy. Overall, 47.2% received 1 prior line of therapy, 28.9% received 2 prior lines, 13.9% received 3 prior lines, and 10.0% received >3 prior lines of therapy. A total of 21.1% of patients were refractory to lenalidomide at their last line of therapy.

Among patients treated with D-Vd, the median duration of treatment was 13.4 months (range: 0-26.7) versus 5.2 months (range: 0.2-8.0) with Vd. Following a protocol amendment after the primary analysis, patients who progressed on Vd had the option to receive daratumumab monotherapy.[13] At a median follow-up of 19.4 months, all patients in both groups had discontinued or completed Vd treatment per protocol; in the D-Vd group, 41% of patients

remained on daratumumab monotherapy. A total of 64 patients in the Vd group opted to receive daratumumab monotherapy following disease progression.

The clinical cut-off date was January 11, 2017. At a median duration of follow-up of 19.4 (range: 0-27.7) months, D-Vd significantly prolonged PFS versus Vd (median: 16.7 versus 7.1 months; HR, 0.31; 95% CI, 0.24-0.39; *P* <0.0001 [**Figure 1A**]), with 18-month PFS rates of 48.0% and 7.9%, respectively. Among response-evaluable patients (D-Vd, n = 240; Vd, n = 234), ORR was significantly improved with D-Vd versus Vd (83.8% versus 63.2%; *P* <0.0001 [**Table 2**]), including higher rates of stringent complete response (CR) (8.8% versus 2.6%), CR or better (28.8% versus 9.8%; *P* <0.0001), and very good partial response or better (62.1% versus 29.1%; *P* <0.0001 [**Table S2**]).

MRD was evaluated for the intent-to-treat population at pre-specified time points using a stringent, unbiased approach with IMWG criteria of a minimum sensitivity threshold of 10^{-5} for next generation sequencing evaluation.[20] At this threshold, 11.6% of D-Vd–treated patients were MRD-negative versus 2.4% of Vd-treated patients (*P* = 0.000034 [**Table 2**]). Consistent findings were observed at a higher sensitivity threshold of 10^{-6} (D-Vd: 4.8%; Vd: 0.8%; *P* = 0.004763). Overall survival (OS) remained immature at the time of this analysis, and survival follow-up will continue until 320 deaths are reported, per protocol.

Subgroup analyses showed the clinical benefit of daratumumab by prolonging PFS and improving ORR and MRD-negativity across all clinical populations [**Table 2** and **Figure 2**]. Patients who received D-Vd at first relapse (D-Vd, n = 122; Vd, n = 113) achieved the greatest

benefit [**Table 2** and **Figure 2**]. In this population, PFS was significantly prolonged with D-Vd versus Vd (median: not reached versus 7.9 months; HR, 0.19; 95% CI, 0.12-0.29; *P* <0.0001 [**Figure 1B]**), an 81% reduction in the risk of disease progression or death with 18-month PFS of 68.0% versus 11.5%, respectively. Among patients with 2 to 3 prior therapy lines (D-Vd, n = 107; Vd, n = 106), PFS was also significantly prolonged with D-Vd versus Vd (median: 9.8 versus 6.3 months; HR, 0.51; 95% CI, 0.36-0.71; *P* <0.0001), with 18-month PFS of 31.2% versus 5.5%, respectively [**Figure 1C**]. Likewise, in patients with 1 to 3 prior lines of therapy (D-Vd, n = 229; Vd, n = 219), D-Vd significantly prolonged PFS versus Vd (median: 18.9 versus 7.3 months; HR, 0.31; 95% CI, 0.24-0.40; *P* <0.0001), with 18-month PFS rates of 51.2% versus 8.7%, respectively [**Figure S2**].

The PFS benefit of daratumumab was maintained in patients who received prior bortezomib (D-Vd, n = 162; Vd, n = 164; median: 12.1 versus 6.7 months; HR, 0.35; 95% CI, 0.26-0.46; *P* <0.0001 [**Figure S3**]), with 18-month PFS rates of 37.9% and 1.8%, respectively. In this subgroup, D-Vd improved ORR (80.5% versus 59.5%) and increased MRD-negative rates (6.2% versus 0.6%) versus Vd [**Table 2**]. Importantly, the PFS benefit of daratumumab was maintained in patients who received prior bortezomib in their only line of therapy (D-Vd, n = 62; Vd, n = 57; median: 19.6 versus 8.0 months; HR, 0.20; 95% CI, 0.12-0.35; *P* <0.0001 [**Figure S4**]), with 18-month PFS rates of 58.1% and 2.1%, respectively.

Patients refractory to lenalidomide at their last prior line of therapy (D-Vd, n = 45; Vd, n = 60) also achieved a significant PFS benefit with D-Vd versus Vd (median: 9.3 versus 4.4 months; HR, 0.36; 95% CI, 0.21-0.63; *P* = 0.0002 [**Figure 2**]), with 18-month PFS rates of 33.5% versus

2.0%, respectively. In this subgroup, D-Vd improved ORR (80.5% versus 50.0%) and increased MRD-negativity (8.9% versus 0%) versus Vd [**Table 2**].

In a pre-specified subgroup analysis of cytogenetic risk, D-Vd prolonged PFS and improved ORR versus Vd [**Table 2, Figures 2 and 3A**]. PFS was prolonged with D-Vd versus Vd in both high-risk (median: 11.2 versus 7.2 months; HR: 0.45; 95% CI, 0.25-0.80; *P* = 0.0053; D-Vd, n = 44; Vd, n = 51) and standard-risk disease (median: 19.6 versus 7.0 months; HR: 0.26; 95% CI, 0.18-0.37; *P* <0.0001; D-Vd, n = 123; Vd, n = 135 [**Figures 2 and 3A**]). ORRs were higher with D-Vd for both high-risk (D-Vd, n = 44; Vd, n = 47; 81.8% versus 61.7%; *P* = 0.2028) and standard-risk subgroups (D-Vd, n=118; Vd, n = 131; 84.7% versus 64.1%; *P* = 0.0001 [**Table 2**]). Higher D-Vd response rates aligned with MRD-negativity. In the D-Vd group, 13.8% (17/123) of evaluable, standard-risk patients reached MRD-negativity at 10^{-5} sensitivity versus 2.2% (3/135) in the Vd group (*P* = 0.0003 [**Table 2**]). No high-risk Vd group patients (n = 51) achieved MRD negativity at 10^{-5}, unlike 13.6% (6/44) of high-risk D-Vd group patients (*P* = 0.0018). The PFS benefit of D-Vd versus Vd was also maintained irrespective of the time since last therapy (≤12, >12, ≤6, or >6 months [**Figure 2**]).

Regardless of treatment group, PFS was prolonged in patients who achieved MRD-negative status (median: not reached in either group [**Figure 3B**]). Conversely, among patients with MRD-positive status (10^{-5}), D-Vd significantly prolonged PFS versus Vd (median: not reached versus 16.2 months; HR: 0.19; 95% CI, 0.05 to 0.73; *P* = 0.0080 [**Figure 3B**]). The rate of MRD-negativity (10^{-5}) continued to increase over time for patients in the overall study population who received D-Vd versus Vd (**Figure 4**).

Within the safety population (D-Vd, n = 243; Vd, n = 237), longer follow-up revealed a tolerability profile consistent with the primary analysis and no new emergent toxicities. Among the most common (≥15%) hematologic treatment-emergent adverse events (TEAEs) were thrombocytopenia and anemia. Among the most common (≥15%) non-hematologic TEAEs were peripheral sensory neuropathy, diarrhea, upper respiratory tract infection, and cough [**Table 3**].

The most common (≥5%) grade 3 or 4 hematologic TEAEs included thrombocytopenia, anemia, neutropenia, and lymphopenia [**Table 3]**. The most common (≥5%) grade 3 or 4 non-hematological TEAEs included pneumonia, hypertension, and peripheral sensory neuropathy. Discontinuations due to TEAEs remained low and balanced between groups (D-Vd: 9.5%; Vd: 9.3%). Transfusions were received by 26.3% versus 20.3% of patients (D-Vd versus Vd).

With longer follow-up, second primary malignancies (SPMs) occurred in 10 (4.1%) patients who received D-Vd (4 new cases following the primary analysis[13] included basal and squamous cell carcinoma, Bowen disease, and prostate cancer) versus 1 (0.4%) patient who received Vd (no new cases with longer follow-up).

The EORTC QLQ-C30 and EQ-5D-5L tools showed that HRQoL was maintained during treatment for patients in both groups who remained on the study. Significant differences in the least squares mean changes from baseline were not observed between D-Vd and Vd at any time for the EORTC QLQ-C30 Global Health Status Scores or the EQ-5D-5L Utility Score. A significant difference was observed solely at Week 21 in favor of D-Vd for the Visual Analog

Scale Score (P = 0.0185). No significant differences in EORTC QLQ-C30 global health status were observed for median time to improvement (5.0 versus 5.1 months; HR: 0.99; 95% CI, 0.76-1.29; P = 0.9163). Similarly, no significant differences in median time to improvement were observed for either the EQ-5D-5L Utility Score (7.7 versus 3.5 months; HR: 0.82; 95% CI, 0.62-1.08; P = 0.1469) or the Visual Analog Scale Score (5.0 versus 5.0 months; HR: 1.03; 95% CI, 0.79-1.35; P = 0.8072).

DISCUSSION

These data confirm that D-Vd provides significant clinical benefit to patients with RRMM. D-Vd prolonged PFS, resulting in a 69% reduction in the risk of disease progression or death versus Vd. With an additional 12 months of follow-up, responses to daratumumab deepened over time (≥CR: 28.8%) compared with the primary analysis (19.2%).[13] Deeper responses to D-Vd were associated with significantly higher (>4 fold) MRD-negative rates at sensitivities of 10^{-5} and 10^{-6} versus Vd. We hypothesize that as previous studies have demonstrated a correlation between MRD negativity and OS,[21,22] this may translate into improved OS outcomes after longer follow-up for patients treated with D-Vd. Analysis of OS is ongoing.

There were consistent clinical benefits with D-Vd versus Vd across subgroups based on prior lines of therapy, treatment exposure, or refractory status. These were also observed in patients regardless of time since last therapy or cytogenetic risk, patient subgroups that were not evaluated in the primary analysis. Importantly, the benefit of D-Vd was maintained in patients who received prior bortezomib (including as their sole prior line of therapy) and those refractory to lenalidomide at their last prior line of therapy. Bortezomib and lenalidomide-based

combinations are common MM first-line and maintenance regimens. Thus D-Vd can be considered after bortezomib (if patients are not PI-refractory) or in lenalidomide-refractory patients, of particular importance considering the increased lenalidomide use as maintenance therapy in newly diagnosed MM regardless of transplant eligibility.[23,24] D-Vd significantly prolonged PFS versus Vd across all lines of therapy with the greatest benefit achieved in patients who received 1 prior line in comparison to those who received 2-3 or >3 prior lines of therapy. Response rates, including the rates of MRD-negativity were also highest in patients who received 1 prior line of therapy. As D-Vd showed the greatest benefit at first relapse, it may represent an optimal second-line treatment for patients after frontline lenalidomide or bortezomib.

The benefit of D-Vd was also maintained in patients regardless of cytogenetic risk, as D-Vd but not Vd induced MRD-negativity in high-risk patients, suggesting that this combination may improve historically poor outcomes in this population.[25-28]

D-Vd–treated patients continued to receive daratumumab monotherapy after completing 8 cycles of Vd, reflected by the longer treatment duration (median: D-Vd, 13.4 months; Vd, 5.2 months). With longer follow-up, the depth of response in the D-Vd arm, including CR rates and MRD-negativity, continued to improve over time after patients entered the monotherapy phase, supporting the benefit of continued daratumumab treatment. Analyses are ongoing to quantify the therapeutic impact of maintenance therapy with single-agent daratumumab.

This was the first randomized, phase 3 clinical trial of RRMM with prospective MRD evaluation. MRD-negative status was associated with prolonged PFS in both treatment groups, but D-Vd

increased MRD-negative rates at all sensitivity thresholds and evaluated subgroups. Additional longitudinal MRD evaluation in CASTOR is ongoing and the potential benefit of daratumumab-induced MRD negativity is being explored in studies of newly diagnosed MM (ALCYONE [NCT02195479]; MAIA [NCT02252172]; CASSIOPEIA [NCT02541383]) and smoldering MM (AQUILA [NCT03301220]). These studies aim to further validate MRD-negative status as a surrogate study endpoint.

Several new agents for RRMM have been approved based on robust clinical data, including carfilzomib[29] and ixazomib[30] (second-generation PIs), pomalidomide[31,32] (a third-generation immunomodulatory drug), daratumumab[13,14,33-35] and elotuzumab[36] (monoclonal antibodies), and panobinostat[4] (a histone deacetylase inhibitor). Approvals of many of these agents were based on superiority of PFS in phase 3 trials. These studies are beginning to report OS outcomes. In the ENDEAVOR study, carfilzomib and dexamethasone conferred an additional OS benefit of 7.6 months versus Vd.[37] OS analysis in CASTOR is ongoing.

Clinical trials are not usually powered to determine optimal treatment sequencing or the most effective regimen for each disease subset.[38] Although meta-analyses provide useful guides for selecting treatment options, physicians need to consider many different factors to optimize individual regimens including numbers and types of prior regimens, duration of response to prior therapy, toxicities with prior therapies, disease aggressiveness, and performance status or frailty.[38,39] Based on the current findings, and others,[40] daratumumab combined with other anti-myeloma drugs such as bortezomib or lenalidomide may provide significant benefit in patients

with early relapsed MM regardless of prior treatment exposure. It remains to be seen whether this translates to prolonged survival.

The safety profile of D-Vd remained unchanged with approximately 1 year of additional follow-up from the primary analysis,[13] with no new unexpected TEAEs observed. Preliminary data indicated that adding a third agent to Vd did not worsen HRQoL, an evaluation that was not presented in the primary analysis. More SPMs were reported with D-Vd versus Vd (4.1% versus 0.4%); this rate is similar to the incidence of SPMs reported for patients in POLLUX (5.7% for both D-Rd and Rd; manuscript in preparation) and for RRMM patients in general (between 1-6%).[41] At clinical cut-off, all patients in the Vd group had discontinued or completed 8 treatment cycles, whereas 41% of patients receiving D-Vd remained on daratumumab treatment. Therefore, more frequent monitoring during active treatment may explain why a greater number of TEAEs (including grade 3 or 4 events) and SPMs were reported with D-Vd. After 8 cycles of D-Vd, patients were monitored every 4 weeks during daratumumab dosing, whereas patients who received Vd who did not receive daratumumab monotherapy were followed for survival via phone calls every 16 weeks following disease progression.

In conclusion, the original finding of significant benefit of D-Vd over Vd was confirmed regardless of treatment history or cytogenetic risk. Importantly, this clinical benefit was achieved without any emergent safety issues or decline in HRQoL. These results provide further support for the addition of daratumumab to a standard of care regimen in RRMM, particularly at first relapse. The CASTOR study is ongoing and the feasibility of MRD-negativity as a surrogate for

OS in RRMM continues to be investigated. An analysis of OS will be conducted after 320 events are observed.

AUTHOR CONTRIBUTION

All authors were involved in the study design and/or data interpretation, and drafting, critically reviewing, and revising the manuscript. AS, SL, KW, T Mark, IS, T Masszi, BL, M-DL, AB, VH, MC, J-JL, AKN, HQ, CL, WB, PC, C-KM, ECS, AAC-K, NH, MC, MB, RO, J-CJ, H-JS, PS, and M-VM contributed to the accrual and treatment of patients. HA-L, DS, TC, CC, HA, MQ, PT, AKS, and JS collected and/or analyzed the data. All authors approved submitting the manuscript for publication, and being accountable for the accuracy and integrity of the study.

ACKNOWLEDGMENTS

This study was sponsored by Janssen Research & Development, LLC. The authors wish to thank the patients participating in this study and their families, as well as the global network of investigators, research nurses, study coordinators, and operations staff (including Xiang Qin, Jaime Bald, and Christopher Velas). Medical writing and editorial support were provided by Jason Jung, PhD and Kristin Runkle, PhD of MedErgy, and were funded by Janssen Global Services, LLC. 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.

REFERENCES

1. Kurtin SE. Relapsed or relapsed/refractory multiple myeloma. J Adv Pract Oncol. 2013;4(Suppl 1):5-14.
2. Merin NM, Kelly KR. Clinical use of proteasome inhibitors in the treatment of multiple myeloma. Pharmaceuticals (Basel). 2015;8(1):1-20.
3. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17(1):27-38.
4. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195-1206.
5. San-Miguel JF, Hungria VTM, Yoon SS, et al. Final analysis of overall survivial from the Phase 3 panorama 1 trial of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or replased and refractory multiple myeloma. Blood. 2015;126(23):3026.
6. Jakubowiak A, Offidani M, Pegourie B, et al. Randomized phase 2 study of elotuzumab plus bortezomib/dexamethasone (Bd) versus Bd for relapsed/refractory multiple myeloma. Blood. 2016;127(33):2833-2840.
7. 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. 2011;186(3):1840-1848.
8. 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. 2014;124(21):3474.
9. Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7(2):311-321.
10. Overdijk MB, Jansen JH, Nederend M, et al. The therapeutic CD38 monoclonal antibody daratumumab induces programmed cell death via Fcgamma receptor-mediated cross-linking. J Immunol. 2016;197(3):807-813.
11. van de Donk NWCJ, Janmaat ML, Mutis T, et al. Monoclonal antibodies targeting CD38 in hematological malignancies and beyond. Immunol Rev. 2016;270(1):95-112.
12. Krejcik 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. 2016;128(3):384-394.
13. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(8):754-766.
14. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(14):1319-1331.
15. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc.;2018.

16. European Medicines Agency. DARZALEX summary of product characteristics, May 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf. Last accessed July 2018.
17. Durie BGM, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-1473.
18. 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. 2011;117(18):4691-4695.
19. Chiu C, Soong D, Spicka I, et al. Next generation sequencing (NGS) methodology for determining cytogenetic risk status in the daratumumab phase 3 CASTOR and POLLUX studies in relapsed or refractory multiple myeloma (RRMM). Presented at: the 22nd Congress of the European Hematology Association (EHA); June 22-25, 2017; Madrid, Spain. Abstract S100.
20. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-346.
21. Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood. 2014;123(20):3073-3079.
22. Rawstron AC, Gregory WM, de Tute RM, et al. Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. Blood. 2015;125(12):1932-1935.
23. McCarthy PL, Palumbo A. Maintenance therapy for multiple myeloma. Hematol Oncol Clin North Am. 2014;28(5):839-859.
24. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-917.
25. Dimopoulos MA, Weisel KC, Song KW, et al. Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. Haematologica. 2015;100(10):1327-1333.
26. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood. 2007;109(8):3489-3495.
27. Avet-Loiseau H, Hulin C, Campion L, et al. Chromosomal abnormalities are major prognostic factors in elderly patients with multiple myeloma: the intergroupe francophone du myelome experience. J Clin Oncol. 2013;31(22):2806-2809.
28. Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014;28(2):269-277.
29. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142-152.
30. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621-1634.
31. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123(12):1826-1832.
32. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple

myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-1066.
33. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med. 2015;373(13):1207-1219.
34. Lonial S, Weiss BM, Usmani S, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016;387(10027):1551-1560.
35. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017;130(8):974-981.
36. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015;373(7):621-631.
37. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. The Lancet Oncology. 2017;18:1327-1337.
38. Boudreault JS, Touzeau C, Moreau P. Triplet combinations in relapsed/refractory myeloma: update on recent phase 3 trials. Expert Rev Hematol. 2017;10(3):207-215.
39. Yee AJ, Raje NS. Sequencing of nontransplant treatments in multiple myeloma patients with active disease. Hematology Am Soc Hematol Educ Program. 2016;2016(1):495-503.
40. van Beurden-Tan CH, Franken MG, Blommestein HM, Uyl-de Groot CA, Sonneveld P. Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma. J Clin Oncol. 2017;35:1313-1319.
41. Areethamsirikul N, Reece DE. The risk of secondary primary malignancies after therapy for multiple myeloma. Leuk Lymphoma. 2015;56(11):3012-3021.

Table 1. Baseline Demographics and Clinical Characteristics of the Intention-to-treat Population

Characteristic	D-Vd (n = 251)	Vd (n = 247)
Age (years)	64 (30-88)	64 (33-85)
Median time from diagnosis (years)	3.9	3.7
Number of prior lines of therapy, n (%)		
Median (range)	2 (1-9)	2 (1-10)
1	122 (48.6)	113 (45.7)
2 to 3	107 (42.6)	106 (42.9)
>3	22 (8.8)	28 (11.3)
1 to 3	229 (91.2)	219 (88.7)
Prior treatments, n (%)		
PI	169 (67.3)	172 (69.6)
Bortezomib	162 (64.5)	164 (66.4)
IMiD	179 (71.3)	198 (80.2)
Thalidomide	125 (49.8)	121 (49.0)
Lenalidomide	89 (35.5)	120 (48.6)
PI and IMiD	112 (44.6)	129 (52.2)
Prior ASCT, n (%)	157 (62.5)	149 (60.3)
Refractory to last line of therapy, n (%)	76 (30.3)	85 (34.4)
Refractory to lenalidomide at last prior line of therapy, n (%)	45 (17.9)	60 (24.3)
Time since last prior line of treatment, n (%)		
>12 months	118 (47.0)	104 (42.1)
≤12 months	133 (53.0)	143 (57.9)
>6 months	150 (59.8)	133 (53.8)
≤6 months	101 (40.2)	114 (46.2)
Cytogenetic profile, n (%)[a]		
n	167	186
Standard-risk	123 (73.7)	135 (72.6)
High-risk	44 (26.3)	51 (27.4)

PI, proteasome inhibitor; IMiD, immunomodulatory drug; ASCT, autologous stem cell transplantation; D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.
Data are median (range) or n (%).
[a]Cytogenetic status was determined using next-generation sequencing. High-risk cytogenetic status was defined as having at least one of the following abnormalities: del17p, t(4:14), or t(14:16); standard-risk cytogenetic status was defined as those who underwent cytogenetic testing and did not meet the high-risk criteria.

Table 2. Overall Response Rate and Minimal Residual Disease Based on Prior Treatment History

	# of patients in group		Overall response rate n (%)[a]			# of patients in group		Minimal residual disease n (%)[b]					
								10^{-5}			10^{-6}		
Subgroup	**D-Vd**	**Vd**	**D-Vd**	**Vd**	***P*-value[c]**	**D-Vd**	**Vd**	**D-Vd**	**Vd**	***P*-value[d]**	**D-Vd**	**Vd**	***P*-value[d]**
ITT	240	234	201 (83.8)	148 (63.2)	<0.0001	251	247	29 (11.6)	6 (2.4)	0.000034	12 (4.8)	2 (0.8)	0.004763
Prior lines of therapy													
1	119	109	108 (90.8)	81 (74.3)	0.0014	122	113	17 (13.9)	3 (2.7)	0.001138	8 (6.6)	2 (1.8)	0.059541
2 to 3	99	100	78 (78.8)	58 (58.0)	0.0022	107	106	12 (11.2)	3 (2.8)	0.013511	4 (3.7)	0 (0)	0.018130
>3	22	25	15 (68.2)	9 (36.0)	0.0294	22	28	N/A	N/A	N/A	N/A	N/A	N/A
1 to 3	218	209	186 (85.3)	139 (66.5)	<0.0001	229	219	29 (12.7)	6 (2.7)	<0.0001	12 (5.2)	2 (0.9)	0.0055
Prior therapy													
Bortezomib	154	153	124 (80.5)	91 (59.5)	<0.0001	162	164	10 (6.2)	1 (0.6)	0.002822	5 (3.1)	0 (0)	0.007830
Lenalidomide	83	112	65 (78.3)	59 (52.7)	<0.0001	89	120	7 (7.9)	2 (1.7)	0.0278	2 (2.2)	0 (0)	0.0636
Thalidomide	120	115	102 (85.0)	74 (64.3)	0.0003	125	121	16 (12.8)	4 (3.3)	0.0049	6 (4.8)	2 (1.7)	0.1544
Refractory to lenalidomide at last prior line of therapy	41	58	33 (80.5)	29 (50.0)	0.0021	45	60	4 (8.9)	0 (0)	0.008194	1 (2.2)	0 (0)	0.191319
Treatment-free interval													
≤12 months	125	135	96 (76.8)	66 (48.9)	<0.0001	133	143	13 (9.8)	1 (0.7)	0.0002	4 (3.0)	0 (0)	0.0151
>12 months	115	99	105 (91.3)	82 (82.8)	0.0632	118	104	16 (13.6)	5 (4.8)	0.0223	8 (6.8)	2 (1.9)	0.0704
≤6 months	94	107	72 (76.6)	50 (46.7)	<0.0001	101	114	8 (7.9)	1 (0.9)	0.0067	3 (3.0)	0 (0)	0.0323
>6 months	146	127	129 (88.4)	98 (77.2)	0.0139	150	133	21 (14.0)	5 (3.8)	0.0020	9 (6.0)	2 (1.5)	0.0413
Cytogenetic risk[e]													
High[f]	44	47	36 (81.8)	29 (61.7)	0.2028	44	51	6 (13.6)	0 (0)	0.0018	5 (11.4)	0 (0)	0.0046
Standard	118	131	100 (84.7)	84 (64.1)	0.0001	123	135	17 (13.8)	3 (2.2)	0.0003	6 (4.9)	1 (0.7)	0.0328

D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; ITT, intent-to-treat; N/A, not available.
Data are n (%) based on computerized algorithm.
[a]Response-evaluable population.
[b]ITT population.
[c]*P*-value was generated using the Cochran-Mantel-Haenszel chi-square test.
[d]*P*-value was generated using the likelihood-ratio chi-square test.
[e]Biomarker risk-evaluable population.
[f]Includes subjects who have either del17p, t(14;16), t(4;14), or a combination of these.

Table 3. Adverse Events in the Safety Population

	D-Vd (n = 243)		Vd (n = 237)	
Common hematologic adverse events	All-grade ≥15%	Grade 3 or 4 ≥5%	All-grade ≥15%	Grade 3 or 4 ≥5%
Thrombocytopenia	145 (59.7%)	111 (45.7%)	105 (44.3%)	78 (32.9%)
Anemia	69 (28.4%)	37 (15.2%)	75 (31.6%)	38 (16.0%)
Neutropenia	46 (18.9%)	33 (13.6%)	23 (9.7%)	11 (4.6%)
Lymphopenia	32 (13.2%)	24 (9.9%)	9 (3.8%)	6 (2.5%)
Common non-hematologic adverse events				
Peripheral sensory neuropathy	121 (49.8%)	11 (4.5%)	90 (38.0%)	16 (6.8%)
Diarrhea	85 (35.0%)	9 (3.7%)	53 (22.4%)	3 (1.3%)
Upper respiratory tract infection	76 (31.3%)	6 (2.5)	43 (18.1%)	1 (0.4%)
Cough	68 (28.0%)	0 (0.0%)	30 (12.7%)	0 (0.0%)
Fatigue	53 (21.8%)	12 (4.9%)	58 (24.5%)	8 (3.4%)
Constipation	53 (21.8%)	0 (0.0%)	38 (16.0%)	2 (0.8%)
Back pain	47 (19.3%)	5 (2.1%)	24 (10.1%)	3 (1.3%)
Dyspnea	46 (18.9%)	9 (3.7%)	21 (8.9%)	2 (0.8%)
Edema peripheral	45 (18.5%)	1 (0.4%)	20 (8.4%)	0 (0.0%)
Pyrexia	43 (17.7%)	3 (1.2%)	28 (11.8%)	3 (1.3%)
Insomnia	42 (17.3%)	2 (0.8%)	36 (15.2%)	3 (1.3%)
Asthenia	24 (9.9%)	2 (0.8%)	37 (15.6%)	5 (2.1%)
Pneumonia	36 (14.8%)	24 (9.9%)	31 (13.1%)	24 (10.1%)
Hypertension	23 (9.5%)	16 (6.6%)	8 (3.4%)	2 (0.8%)

D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.
Data are n (%). Incidences of all-grade and grade 3 or 4 adverse events occurring in at least 15% and 5% of patients in either treatment group are listed, respectively.

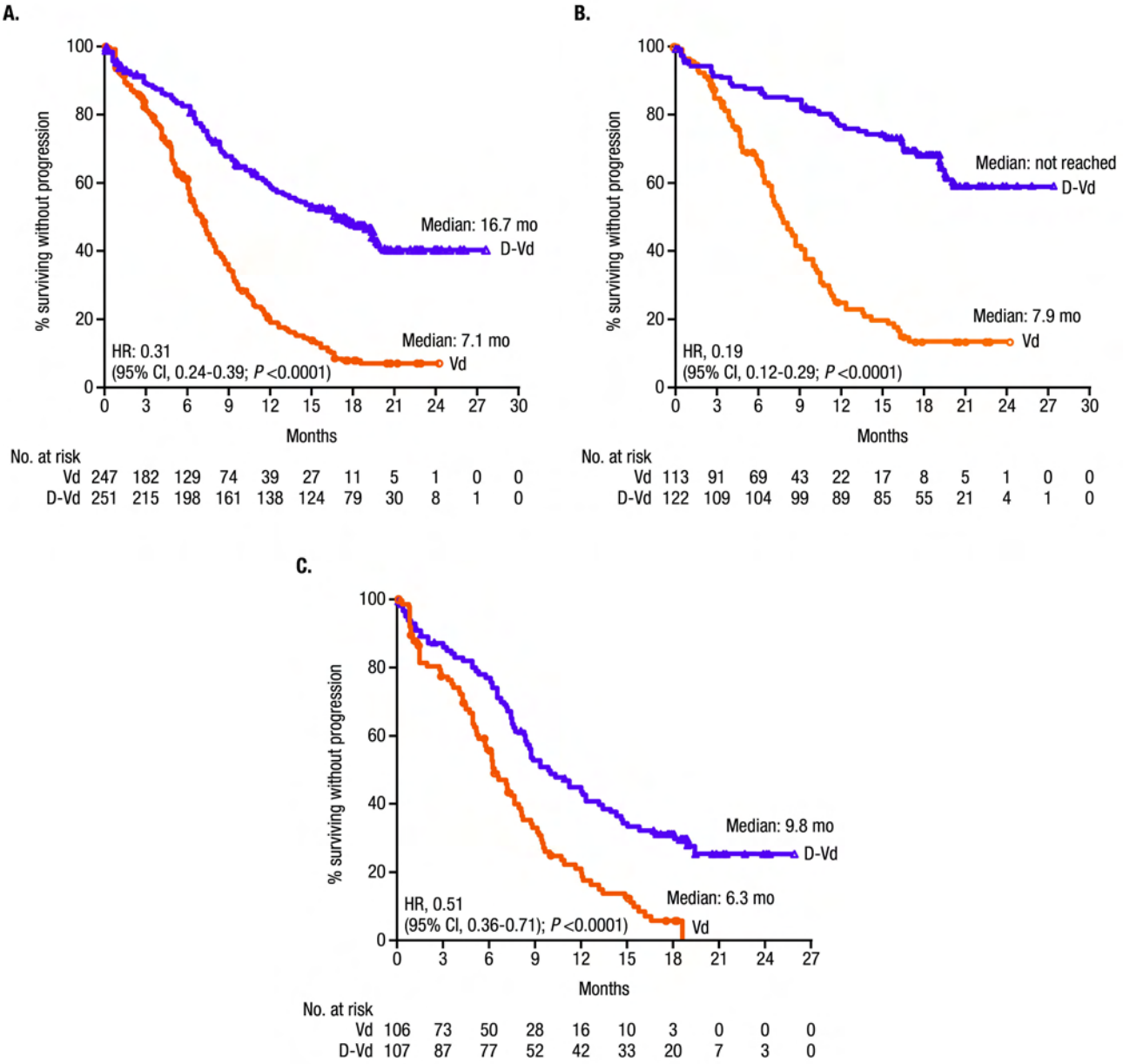
Figure Legends

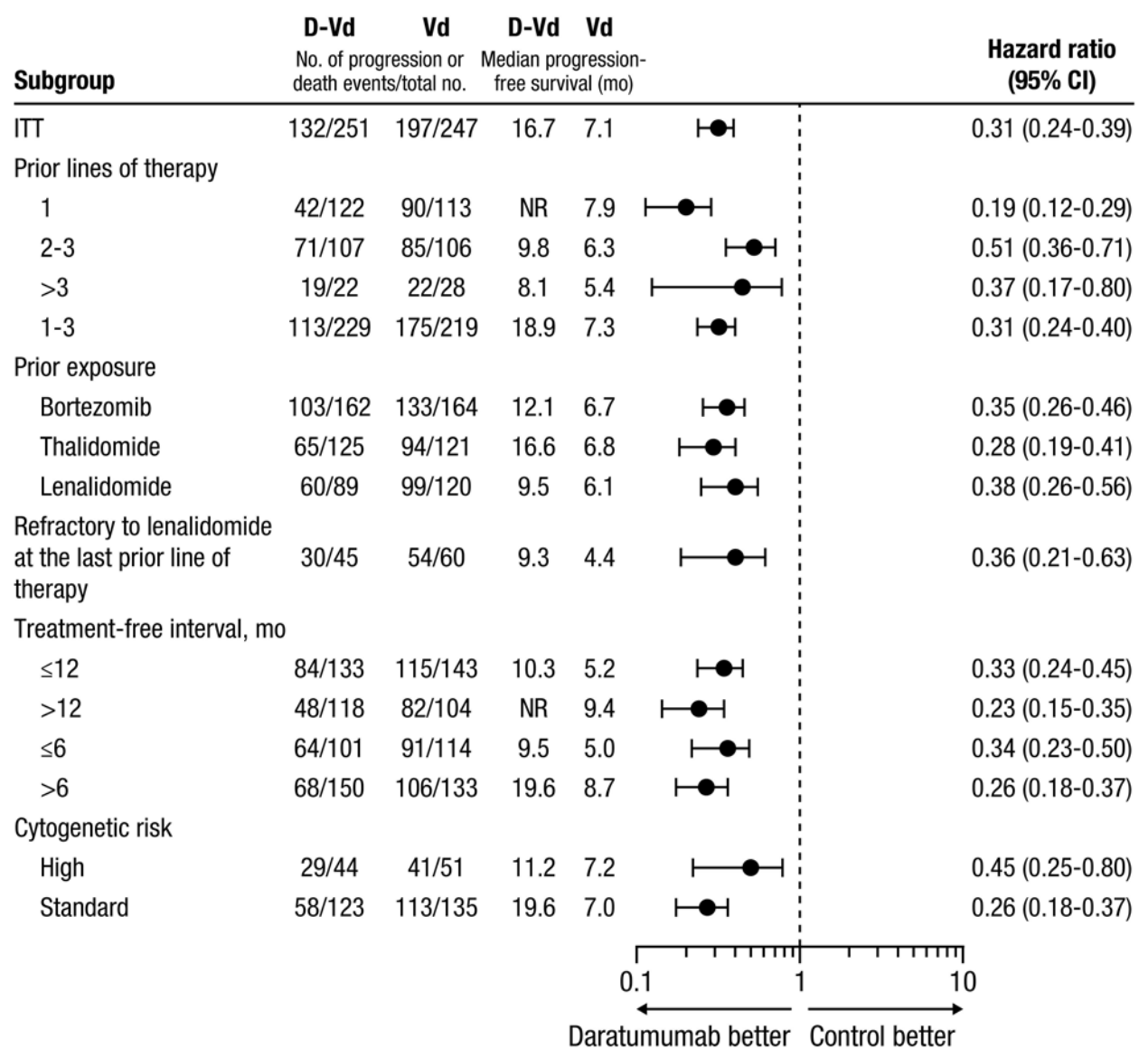
Figure 1. Progression-free survival (A) in the intent-to-treat population and (B) in patients who received 1 prior line of therapy or (C) 2 to 3 prior lines of therapy. Kaplan-Meier curves in (A) the intent-to-treat population and in patients who received (B) 1 prior line of therapy or (C) 2 to 3 prior lines of therapy. D-Vd, daratumumab, bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone, HR, hazard ratio; CI, confidence interval.

Figure 2. Progression-free survival based on prior treatment history and cytogenetic risk (ITT population). Subgroup analysis of progression-free survival based on prior lines of therapy, prior treatment exposure, refractoriness to lenalidomide at the last prior line of therapy, treatment-free interval, and cytogenetic risk. Patients with high-risk cytogenetics had any of t(4;14), t(14;16), or del17p cytogenetic abnormalities as determined by central next-generation sequencing. Standard-risk patients had an absence of high-risk abnormalities. ITT, intent-to-treat; D-Vd, daratumumab, bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone; CI, confidence interval; NR, not reached.

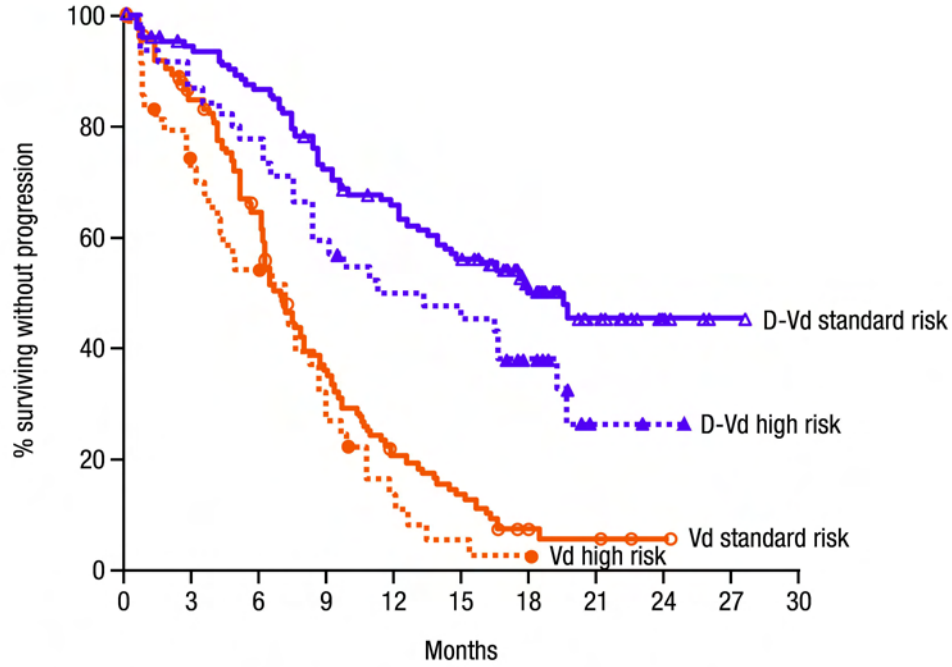
Figure 3. Progression-free survival based on (A) cytogenetic risk and (B) MRD status. (A) Kaplan-Meier estimates of progression-free survival among patients evaluated for cytogenetic risk. High-risk patients had any of t(4;14), t(14;16), or del17p cytogenetic abnormalities as determined by central next-generation sequencing. Standard-risk patients had an absence of high-risk abnormalities. (B) Kaplan-Meier estimates of progression-free survival among patients in the intent-to-treat population. MRD-negative status was evaluated at a sensitivity threshold of 10^{-5} using bone marrow aspirate samples that were prepared using Ficoll and analyzed by the clonoSEQ® assay. MRD, minimal residual disease; D-Vd, daratumumab, bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone.

Figure 4. Time to MRD negativity in the intent-to-treat population. MRD-negative status was evaluated over time at a sensitivity threshold of 10^{-5} using bone marrow aspirate samples that were prepared using Ficoll and analyzed by the clonoSEQ® assay. MRD, minimal residual disease; D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.


A.
% surviving without progression
Median: 16.7 mo
D-Vd
Median: 7.1 mo
Vd
HR: 0.31
(95% CI, 0.24-0.39; P <0.0001)
Months
No. at risk
Vd 247 182 129 74 39 27 11 5 1 0 0
D-Vd 251 215 198 161 138 124 79 30 8 1 0
B.
% surviving without progression
Median: not reached
D-Vd
Median: 7.9 mo
Vd
HR, 0.19
(95% CI, 0.12-0.29; P <0.0001)
Months
No. at risk
Vd 113 91 69 43 22 17 8 5 1 0 0
D-Vd 122 109 104 99 89 85 55 21 4 1 0
C.
% surviving without progression
Median: 9.8 mo
D-Vd
Median: 6.3 mo
Vd
HR, 0.51
(95% CI, 0.36-0.71); P <0.0001)
Months
No. at risk
Vd 106 73 50 28 16 10 3 0 0 0
D-Vd 107 87 77 52 42 33 20 7 3 0

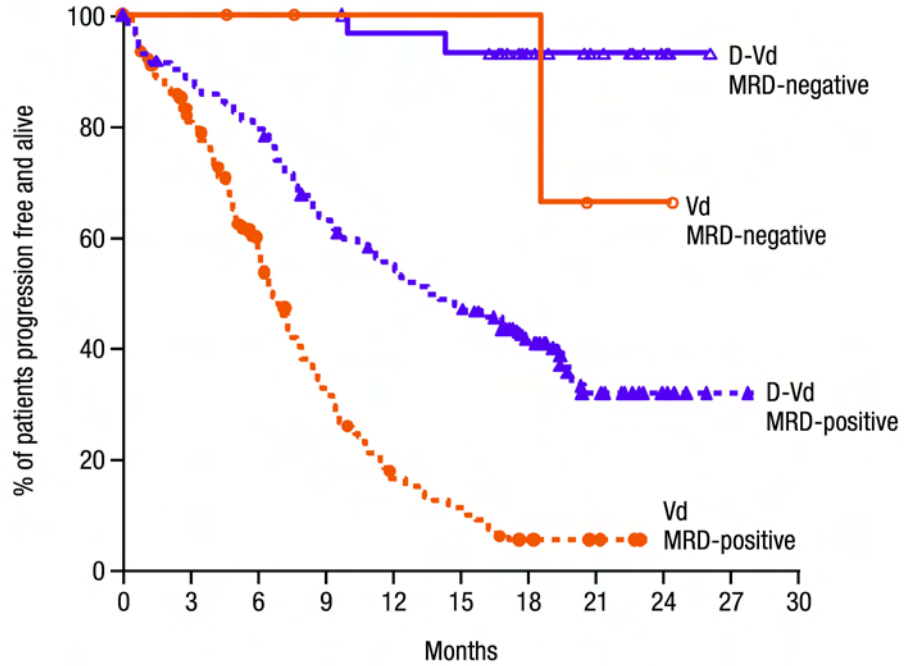

Subgroup
D-Vd
Vd
No. of progression or death events/total no.
D-Vd
Vd
Median progression-free survival (mo)
Hazard ratio (95% CI)
ITT 132/251 197/247 16.7 7.1 0.31 (0.24-0.39)
Prior lines of therapy
1 42/122 90/113 NR 7.9 0.19 (0.12-0.29)
2-3 71/107 85/106 9.8 6.3 0.51 (0.36-0.71)
>3 19/22 22/28 8.1 5.4 0.37 (0.17-0.80)
1-3 113/229 175/219 18.9 7.3 0.31 (0.24-0.40)
Prior exposure
Bortezomib 103/162 133/164 12.1 6.7 0.35 (0.26-0.46)
Thalidomide 65/125 94/121 16.6 6.8 0.28 (0.19-0.41)
Lenalidomide 60/89 99/120 9.5 6.1 0.38 (0.26-0.56)
Refractory to lenalidomide at the last prior line of therapy 30/45 54/60 9.3 4.4 0.36 (0.21-0.63)
Treatment-free interval, mo
≤12 84/133 115/143 10.3 5.2 0.33 (0.24-0.45)
>12 48/118 82/104 NR 9.4 0.23 (0.15-0.35)
≤6 64/101 91/114 9.5 5.0 0.34 (0.23-0.50)
>6 68/150 106/133 19.6 8.7 0.26 (0.18-0.37)
Cytogenetic risk
High 29/44 41/51 11.2 7.2 0.45 (0.25-0.80)
Standard 58/123 113/135 19.6 7.0 0.26 (0.18-0.37)
0.1
1
10
Daratumumab better
Control better

A.

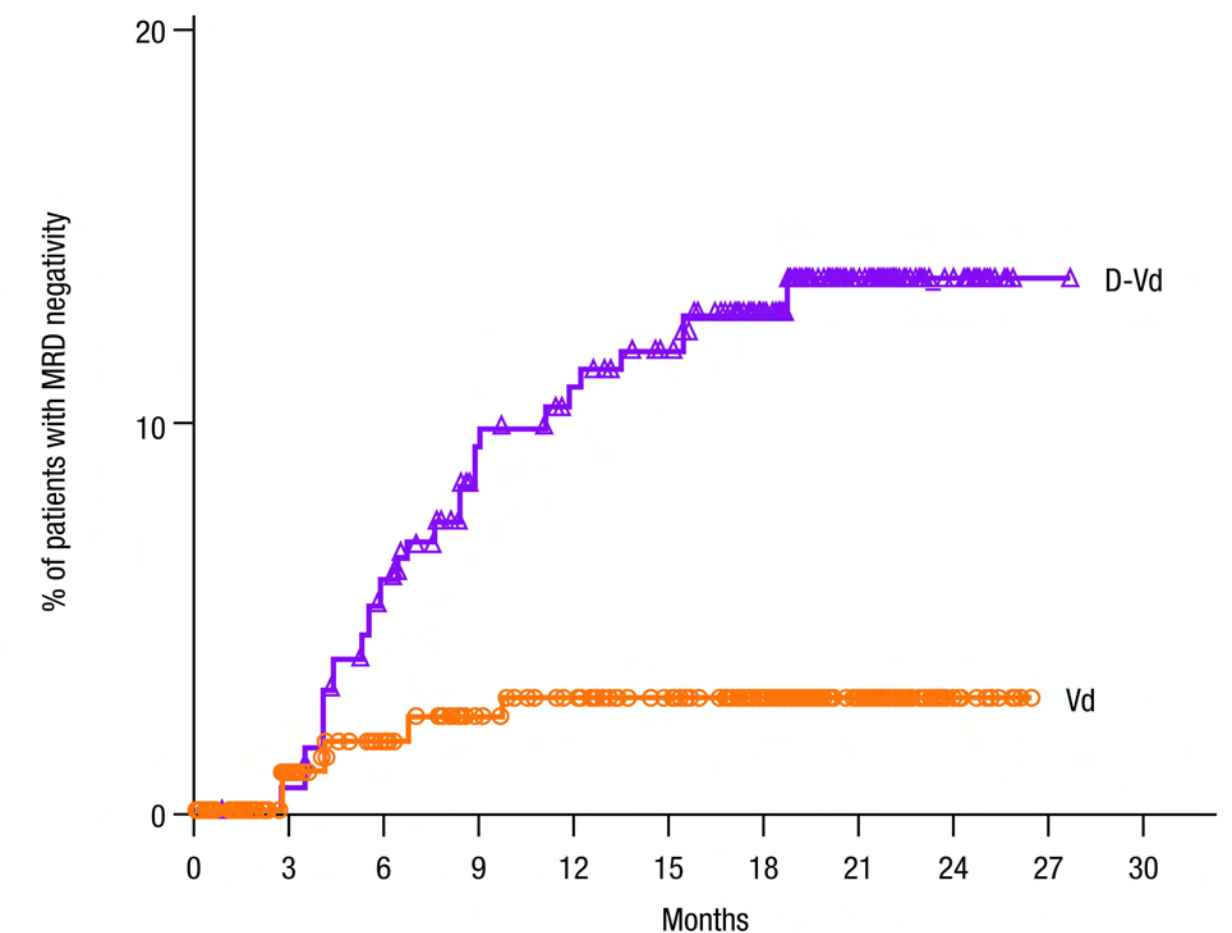


No. at risk											
Vd standard risk	135	106	79	44	25	16	5	3	1	0	0
D-Vd standard risk	123	110	101	83	74	63	36	15	5	1	0
Vd high risk	51	32	23	13	4	2	1	0	0	0	0
D-Vd high risk	44	38	34	26	21	20	11	2	1	0	0

B.



No. at risk											
Vd MRD-neg	6	6	6	6	6	6	5	1	1	0	0
D-Vd MRD-neg	29	29	29	29	27	26	17	11	3	0	0
Vd MRD-pos	241	176	123	68	33	21	6	4	0	0	0
D-Vd MRD-pos	222	186	169	132	111	98	62	19	5	1	0



No. at risk

Vd	247	217	202	187	178	164	125	60	12	0	0
D-Vd	251	229	212	190	183	175	130	56	18	1	0

SUPPLEMENTARY APPENDIX

Supplementary Methods

Cytogenetic abnormalities were determined at the screening visit prior to randomization by centralized next-generation sequencing. High-risk cytogenetic status was defined as having ≥1 of the following abnormalities: del17p, t(4;14), or t(14;16); standard-risk cytogenetic status was defined as those who underwent cytogenetic testing and did not meet the high-risk criteria. For t(4;14), translocations were detected via RNA-seq reads fused between immunoglobulin H and *WHSC1* or *FGFR3*. For t(14;16), translocations involved immunoglobulin H and *WWOX*. Tophat-Fusion[1] and deFuse[2] were used for translocation detection. For del17p detection using exome-seq, a >50% deletion cutoff of the 17p region was utilized with CNVkit[3] and CNV Radar.[4]

Minimal residual disease (MRD) status was assessed by determining the DNA sequence of immunoglobulin genes for patients at the time of suspected complete response (CR; blinded to treatment group) and at 6 and 12 months after first dose (at completion and 6 months after completion of 8 cycles of bortezomib and dexamethasone [Vd] therapy, respectively). MRD was evaluated on bone marrow aspirate samples that had been prepared with Ficoll using the clonoSEQ® assay (Version 1.3; Adaptive Biotechnologies, Seattle, WA, USA) at sensitivities of 0.001% (1 cancer cell per 100,000 nucleated cells or 10^{-5}) and 0.0001% (10^{-6}). To enable for a stringent, unbiased evaluation of MRD, samples from the entire intent-to-treat population that contained ≥1 million cells were assessed; patients were considered MRD-positive if they had only MRD-positive test results or had no MRD assessment. A minimum cell input equivalent to

the given sensitivity threshold was required to determine MRD negativity (for example, MRD at 10^{-6} required that ≥1 million cells were evaluated).

Patient Reported Outcomes

Patient reported outcomes were evaluated in the intent-to-treat population using the EuroQol 5 Dimensions Questionnaire (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life (QoL) Questionnaire Core-30 (EORTC-QLQ-C30). The utility score and visual analog scale were evaluated for EQ-5D-5L. EORTC-QLQ-C30 subscales included the Global Health Status/QoL scale, functional scales (physical, role, cognitive, emotional, and social) and symptom scales (fatigue, pain, and nausea and vomiting). Single-item scores for dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties were also evaluated. Least squares mean changes from baseline were calculated for EQ-5D-5L and EORTC-QLQ-C30 using mixed models for repeated measures.

Statistical Analysis

A total of 498 patients were randomly assigned. Based on an interim analysis after 189 disease progression events had occurred with 7.4 months of follow-up,[5] the independent data and safety monitoring committee recommended that the trial be unblinded early because the prespecified statistical boundary (alpha level of 0.0102) for the primary endpoint was crossed; patients in the control group who had progressed had the option to receive daratumumab monotherapy.

Progression-free survival was compared between treatment groups based on a stratified log-rank test; hazard ratios and 95% confidence intervals 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. A stratified Cochran-Mantel-Haenszel chi-square test was used to test treatment differences in overall response rate and rates of very good partial response or better and CR or better. The MRD-negative rates for each treatment group were compared using the likelihood-ratio chi squared test.

Supplemental Tables

Table S1. Distribution of Cytogenetic Abnormalities (Next generation Sequencing)

	D-Vd (n=167)	Vd (n=186)
del17p, n (%)	13 (7.8)	19 (10.2)
t(4;14), n (%)	26 (15.6)	32 (17.2)
t(14;16), n (%)	7 (4.2)	2 (1.1)

D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

Table S2. Overall Best Confirmed Response in the Response-evaluable Population

Response, n (%)	D-Vd (n = 240)	Vd (n = 234)	*P*-value
ORR	201 (83.8)	148 (63.2)	<0.0001
CR or better	69 (28.8)	23 (9.8)	<0.0001
sCR	21 (8.8)	6 (2.6)	
CR	48 (20.0)	17 (7.3)	
VGPR or better	149 (62.1)	68 (29.1)	<0.0001
VGPR	80 (33.3)	45 (19.2)	
PR	52 (21.7)	80 (34.2)	
MR	9 (3.8)	20 (8.5)	
SD	23 (9.6)	47 (20.1)	
PD	5 (2.1)	16 (6.8)	
NE	2 (0.8)	3 (1.3)	

D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; NE, not evaluated.
Data are n (%) based on computerized algorithm.

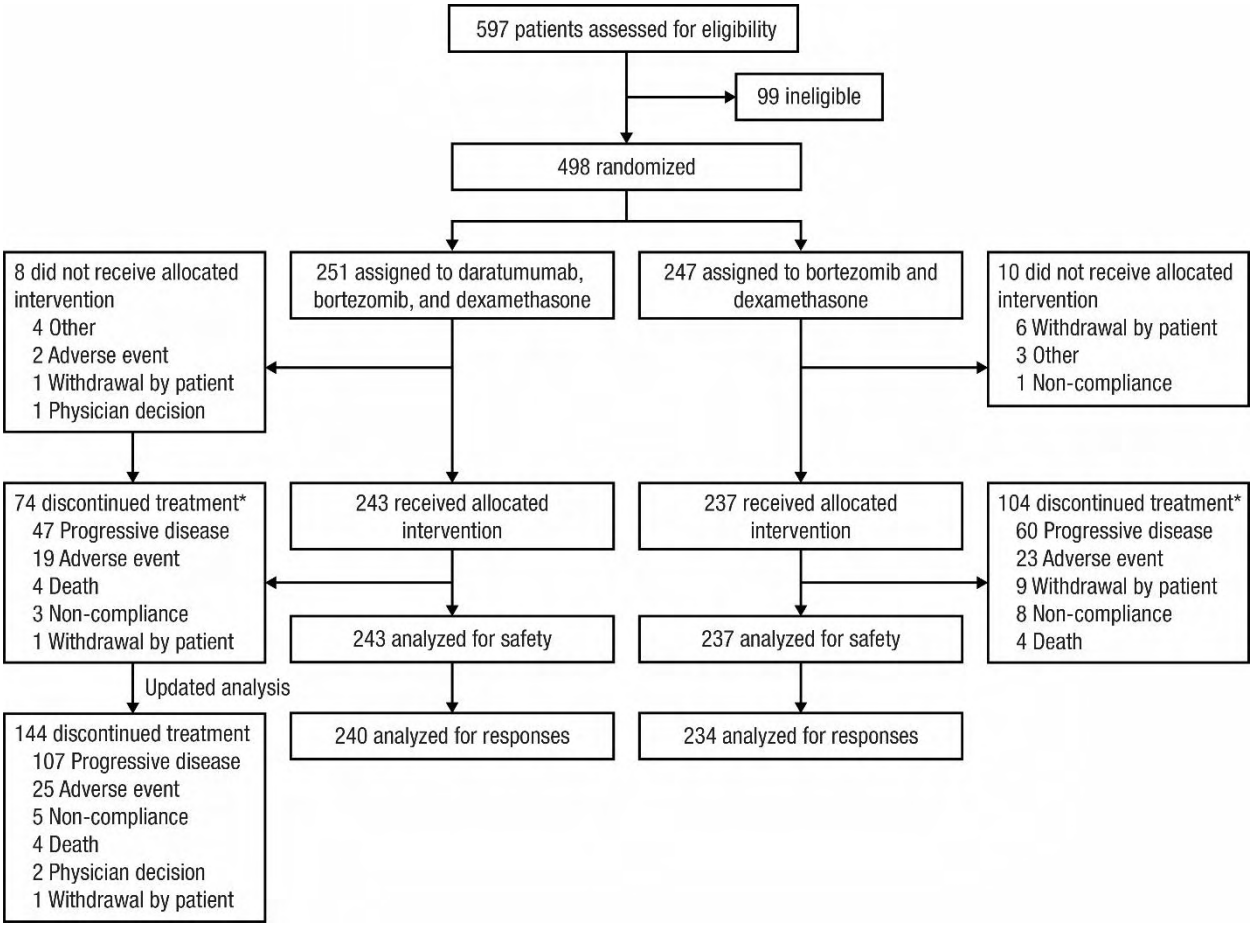


Figure S1. Trial profile. *All patients were to receive 8 cycles of bortezomib and dexamethasone. After Cycle 8, patients in the daratumumab group continued to receive daratumumab monotherapy every 4 weeks, whereas patients receiving only bortezomib and dexamethasone were entered into an observation phase. All patients had discontinued or completed 8 cycles of bortezomib and dexamethasone by the interim analysis.[5] For the updated analysis (clinical cutoff date of January 11, 2017), 99 (41%) patients continued to receive daratumumab monotherapy.

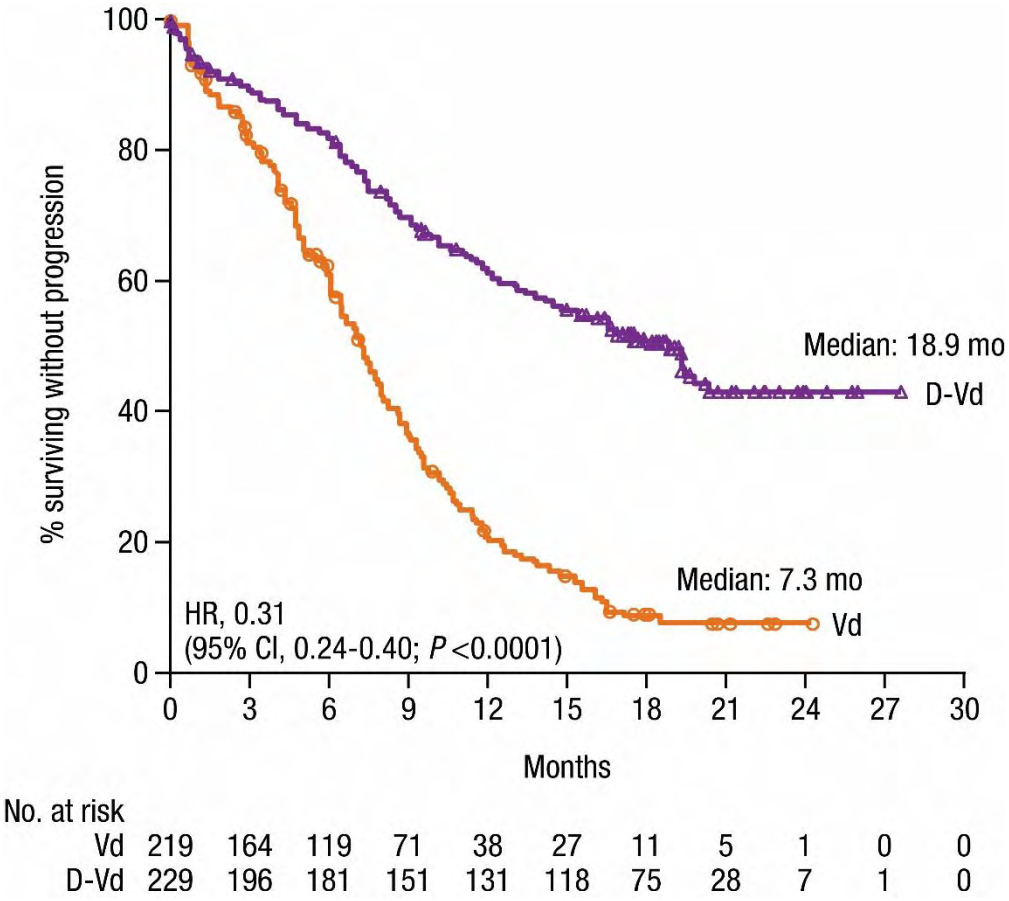


Figure S2. Progression-free survival among patients who received 1 to 3 prior lines of therapy. D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; HR, hazard ratio; CI, confidence interval.

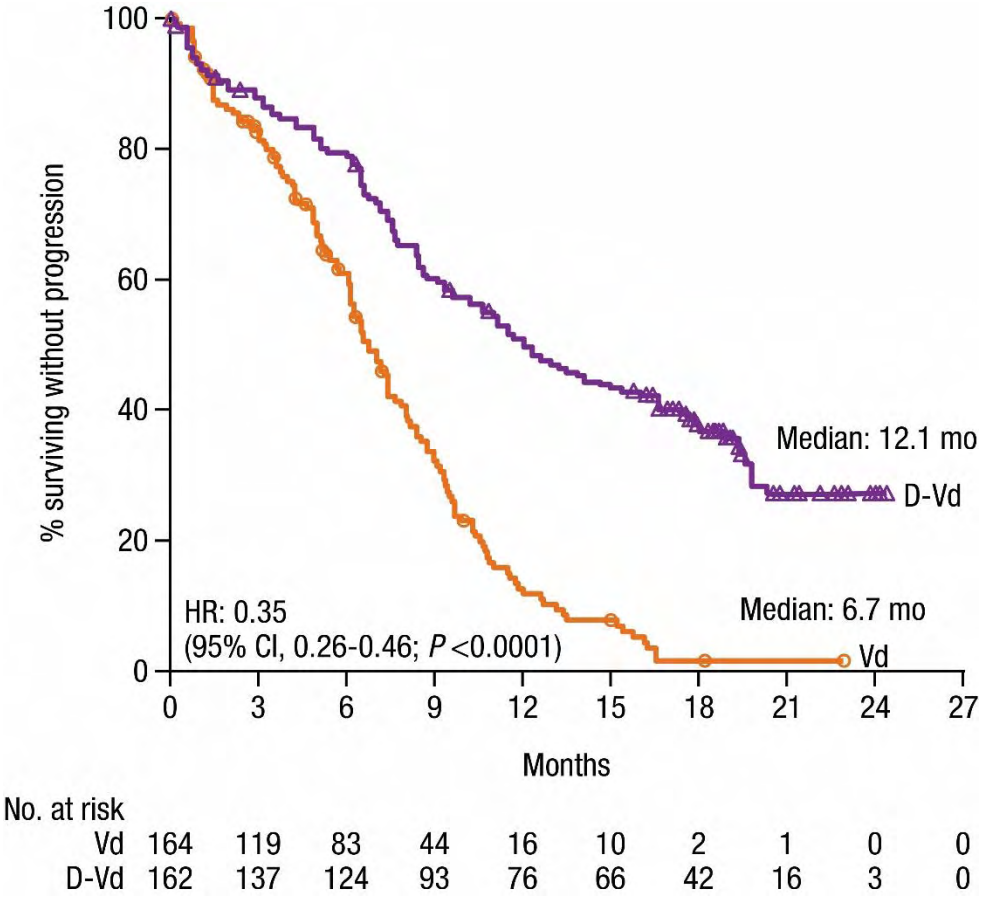


Figure S3. Progression-free survival based on prior bortezomib exposure. D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; HR, hazard ratio; CI, confidence interval.

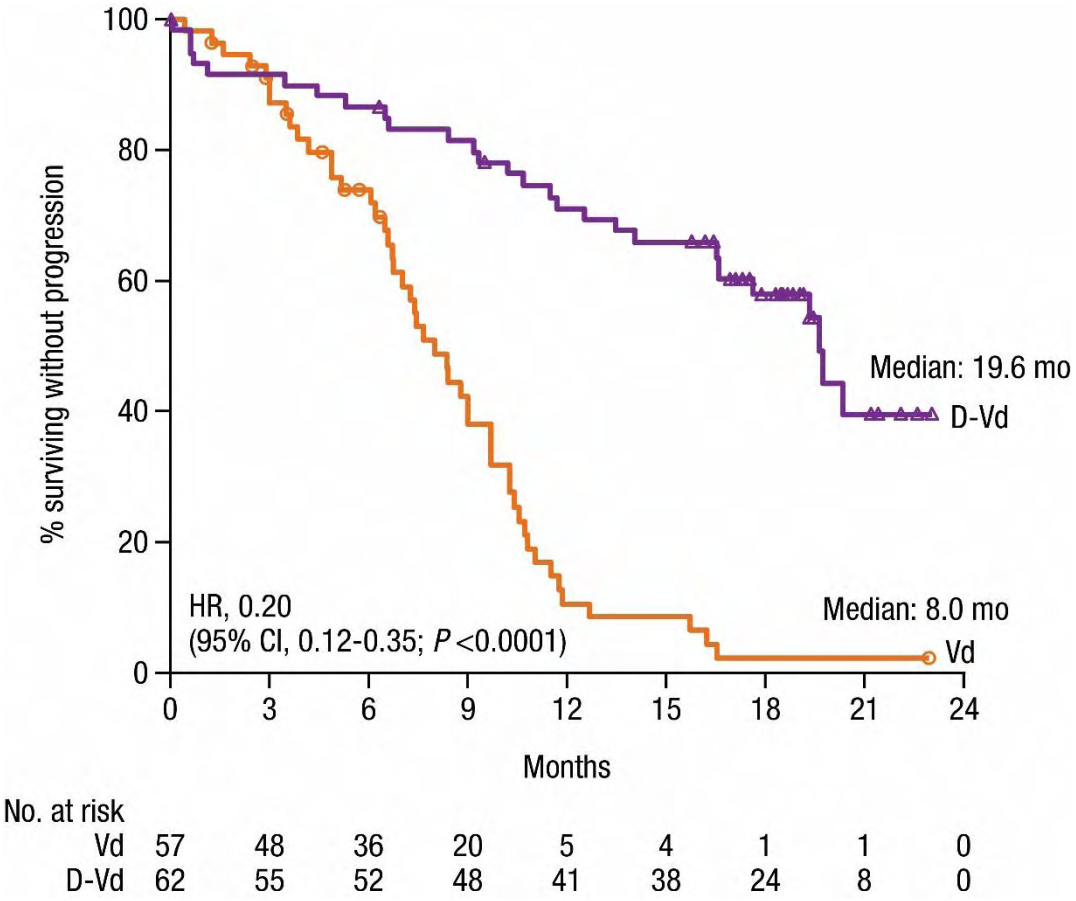


Figure S4. Progression-free survival in patients that received bortezomib in their only line of therapy. D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; HR, hazard ratio; CI, confidence interval.

References

1. Kim D, Salzberg SL. TopHat-Fusion: an algorithm for discovery of novel fusion transcripts. Genome Biol. 2011;12(8):R72.
2. McPherson A, Hormozdiari F, Zayed A, et al. deFuse: an algorithm for gene fusion discovery in tumor RNA-Seq data. PLoS Comput Biol. 2011;7(5):e1001138.
3. Talevich E, Shain AH, Botton T, Bastian BC. CNVkit: Genome-wide copy number detection and visualization from targeted DNA sequencing. PLoS Comput Biol. 2016;12(4):e1004873.
4. Chiu C, Soong D, Spicka I, et al. Next generation sequencing (NGS) methodology for determining cytogenetic risk status in the daratumumab phase 3 CASTOR and POLLUX studies in relapsed or refractory multiple myeloma (RRMM). Presented at: the 22nd Congress of the European Hematology Association (EHA); June 22–25, 2017; Madrid, Spain.
5. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(8):754–766.