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

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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.

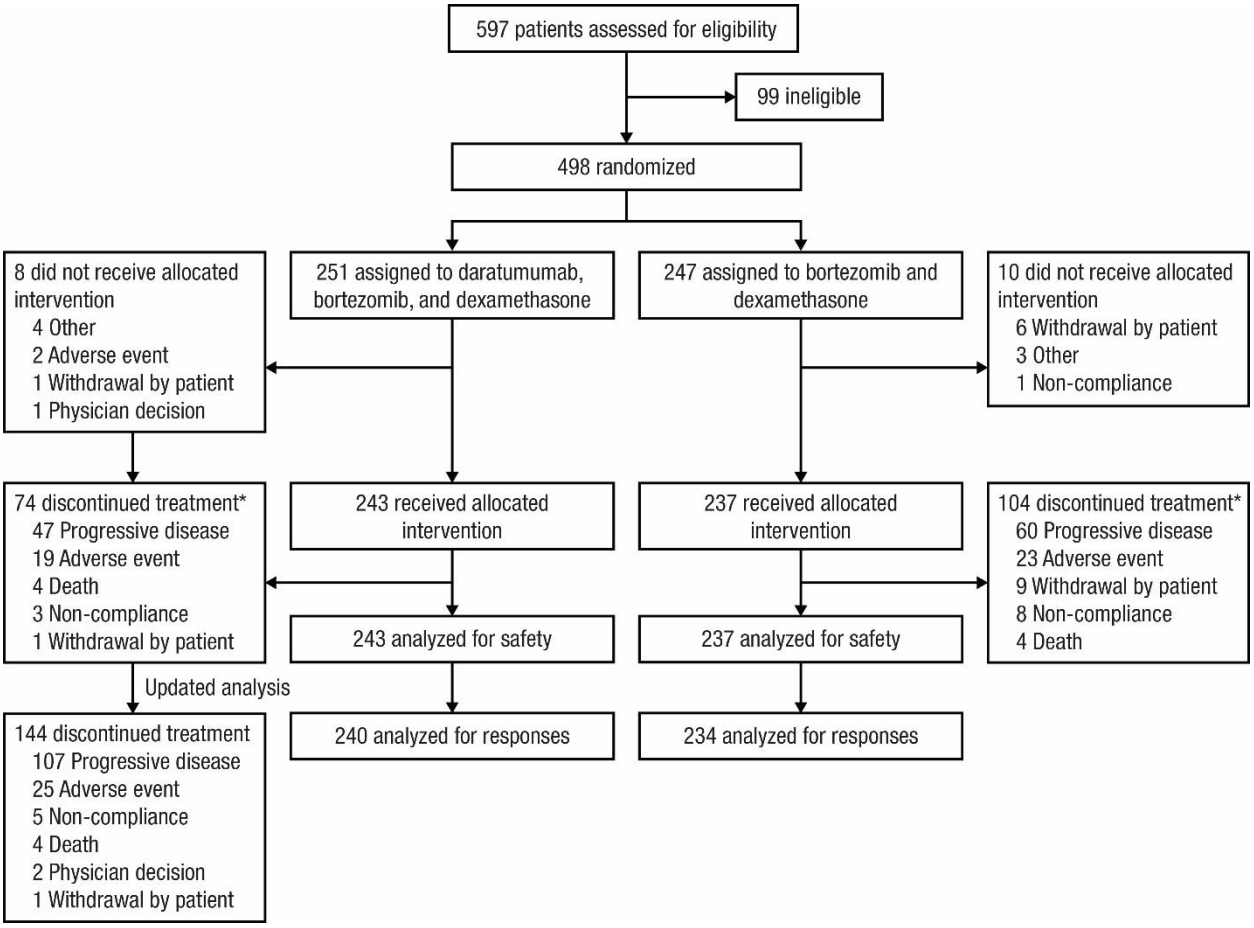


Figure S1. Trial profile. *All patients were to receive 8 cycles of bortezomib and dexamethasone. After Cycle 8, patients in the daratumumab group continued to receive daratumumab monotherapy every 4 weeks, whereas patients receiving only bortezomib and dexamethasone were entered into an observation 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.

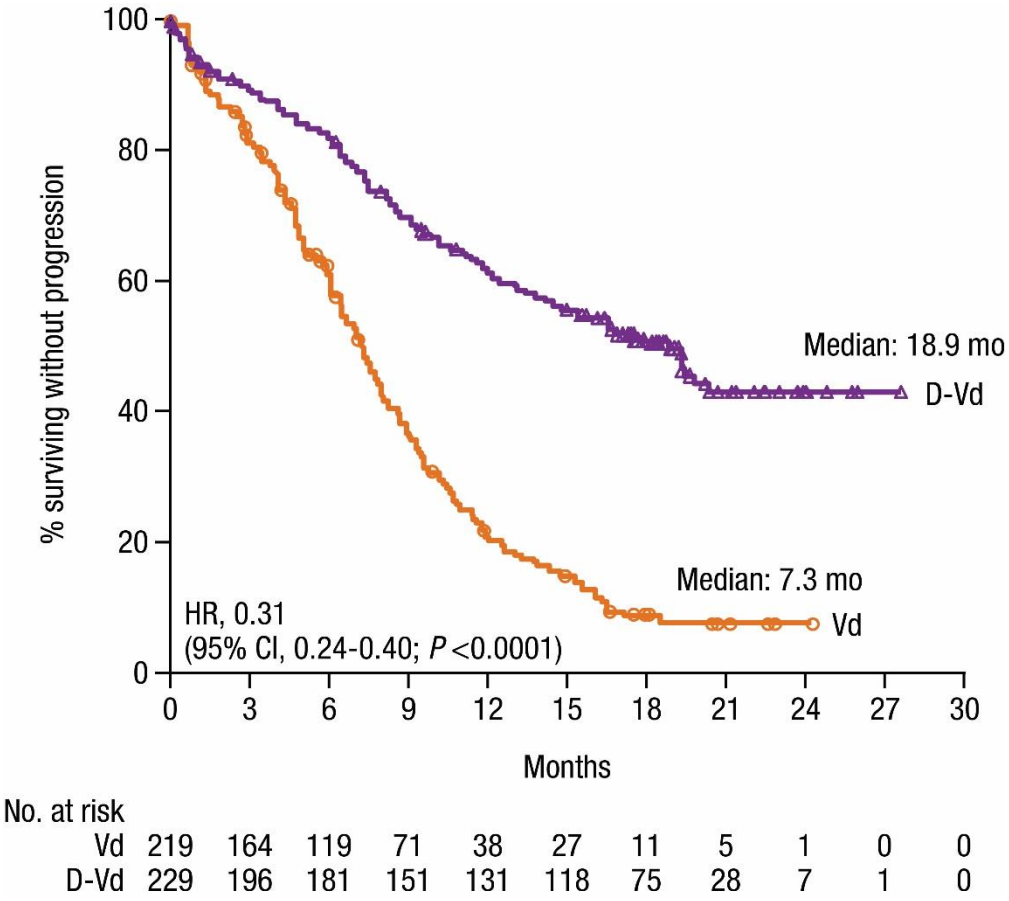
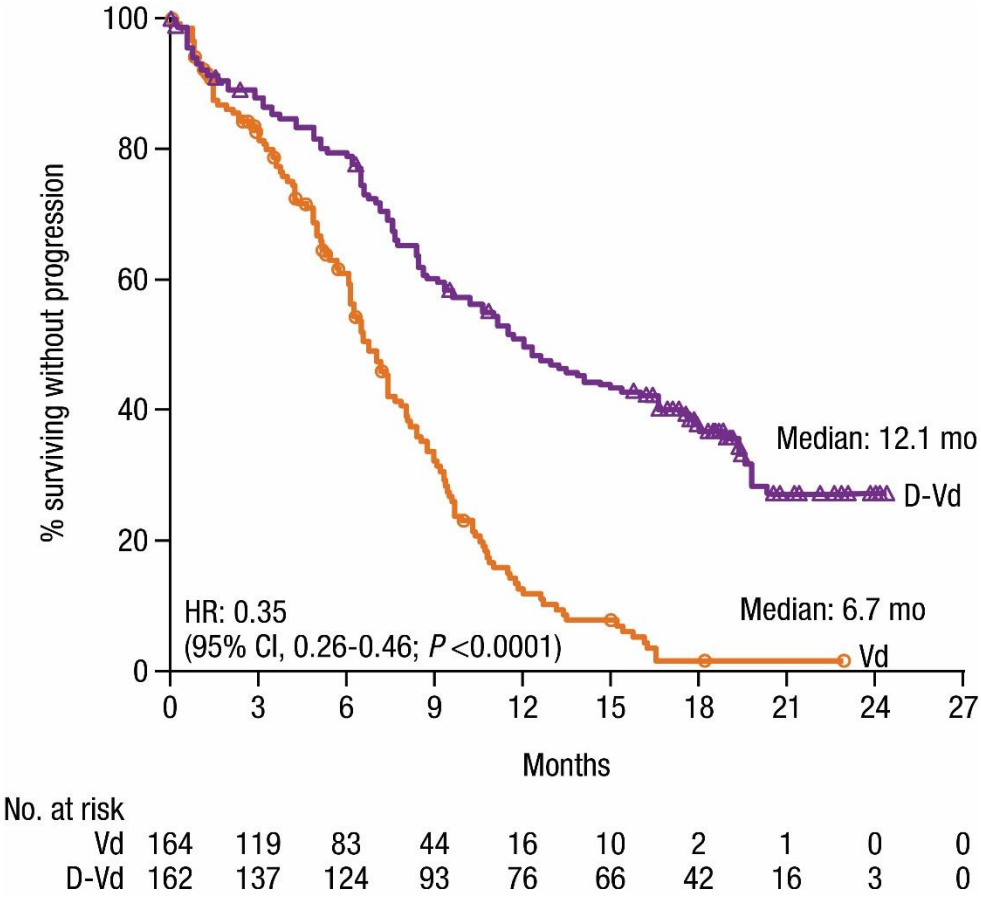


Figure S2. Progression-free survival among patients who received 1 to 3 prior lines of therapy. D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; HR, hazard ratio; CI, confidence interval.



No. at risk

Vd	164	119	83	44	16	10	2	1	0	0
D-Vd	162	137	124	93	76	66	42	16	3	0

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.

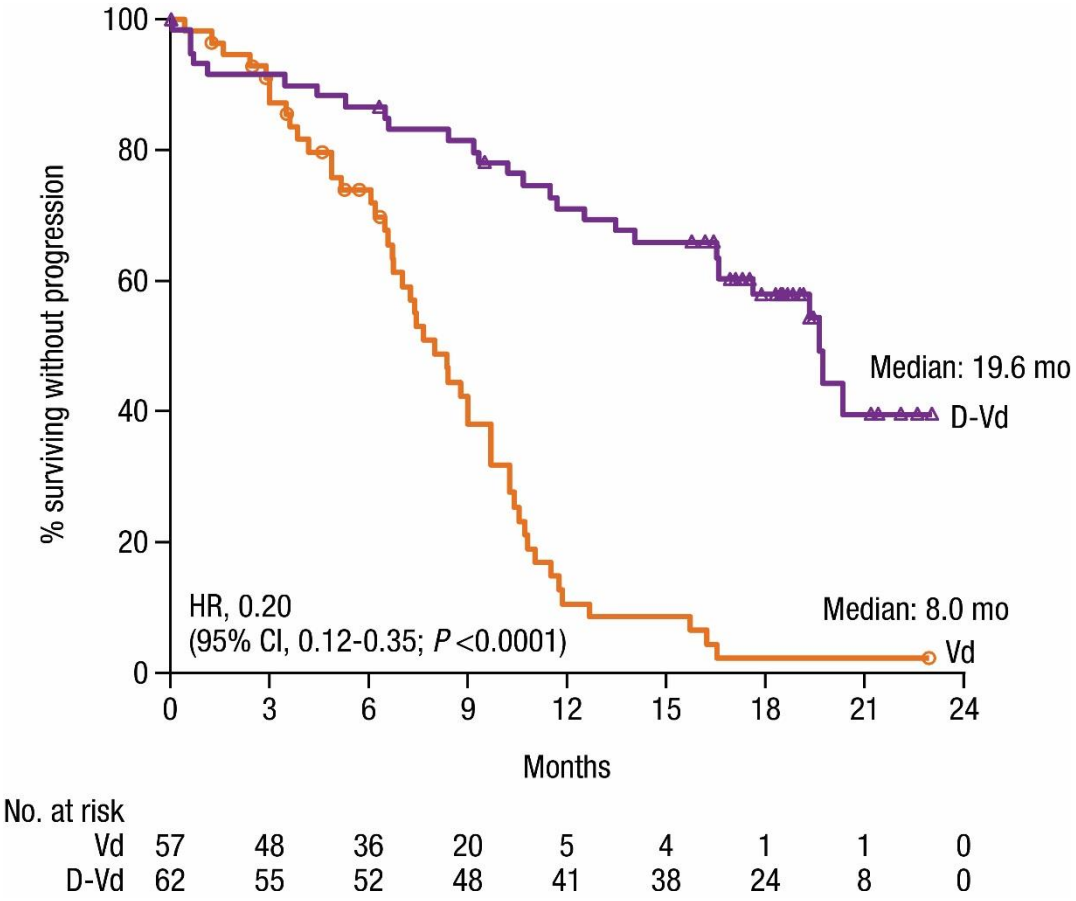


Figure S4. Progression-free survival in patients that received bortezomib in their only line of therapy. D-Vd, daratumumab plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; HR, hazard ratio; CI, confidence interval.

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