Supplementary Appendix

Supplement to: Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, dexamethasone for multiple myeloma. N Engl J Med 2024;390:301-13. DOI: 10.1056/NEJMoa2312054

This appendix has been provided by the authors to give readers additional information about the work.

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Additional Methods

Patients

Eligible patients had newly diagnosed, documented multiple myeloma[1] and were eligible for high-dose therapy and autologous stem cell transplant (ASCT). Patients were 18 to 70 years of age and had an Eastern Cooperative Oncology Group performance status of 0 to 2, an absolute neutrophil count of 1.0×10^9 or more per liter, a hemoglobin level of 7.5 g or more per deciliter, a platelet count of 75×10^9 or more per liter (if ≤50% of bone marrow nucleated cells were plasma cells; otherwise, a platelet count $\geq50\times10^9$ per liter), a calculated creatinine clearance of 30 mL or more per minute, a corrected serum calcium level of 13.5 mg or less per deciliter (≤3.4 mmol per liter), aspartate and alanine aminotransferase levels 2.5 or fewer times the upper limit of normal, and a total bilirubin level 1.5 or fewer times the upper limit of normal. Excluded were patients with prior systemic therapy or stem cell transplant for any plasma cell dyscrasia, grade 2 or higher peripheral neuropathy or neuropathic pain (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5), prior or concurrent invasive malignancy within 5 years of randomization, radiation therapy for treatment of plasmacytoma within 14 days of randomization, plasmapheresis within 28 days of randomization, clinical signs of meningeal involvement of multiple myeloma, pulmonary disease (patients <65 years of age with chronic obstructive pulmonary disease with a forced expiratory volume in 1 second [FEV1] <50% of predicted normal; patients ≥65 years of age with a FEV1 <50% or diffusing capacity of the lungs for carbon monoxide [DLCO] <50%), or moderate or severe persistent asthma within the past 2 years or currently uncontrolled asthma.

Pre- and Post-injection Medications

To decrease the risk of infusion-related reactions, all patients in the group who received daratumumab combined with bortezomib, lenalidomide, and dexamethasone (D-VRd) therapy also received intravenous or oral acetaminophen (650-1000 mg), an antihistamine (intravenous or oral diphenhydramine 25-50 mg or equivalent), and oral montelukast (10 mg, recommended on cycle 1 day 1) up to 3 hours prior to daratumumab injection.

Patients with mild asthma or chronic obstructive pulmonary disease who have a FEV1 of <80% could receive post-infusion medications, including an antihistamine, a leukotriene inhibitor (montelukast or equivalent), a short-acting β2 adrenergic receptor agonist (such as salbutamol), and control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for patients with asthma or long-acting bronchodilators [such as tiotropium or salmeterol] ± inhaled corticosteroids for patients with chronic obstructive pulmonary disease).

Endpoints and Assessments

The primary endpoint was progression-free survival. Key secondary endpoints included overall complete response or better rate, overall minimal residual disease (MRD)–negativity rate, and overall survival. Other secondary endpoints included overall response rate, very good partial response or better rate, stringent complete response rate, and duration of MRD negativity.

Progression-free survival was defined as the time from the date of randomization to the date of first disease progression according to the International Myeloma Working Group response criteria[2] or death due to any cause, whichever occurred earlier.

Overall complete response or better rate was defined as the percentage of patients in the intention-to-treat population who achieved complete response or stringent complete response status at any time during the study per the International Myeloma Working Group criteria.[2] In addition, the specific response must have been achieved prior to the start of subsequent therapies.

Overall MRD-negativity rate was defined as the proportion of patients in the intention-to-treat population who achieved both MRD negativity (at or below a sensitivity threshold of 10^{-5}) by bone marrow aspirate and a complete response or better at any time after the date of randomization during the study (and prior to disease progression, receipt of subsequent therapy, or both). Patients whose tested samples were found to be MRD positive or ambiguous and patients who were not tested were considered as not achieving MRD negativity.

Overall survival was measured from the date of randomization to the date of death due to any cause. Patients who were lost to follow-up were censored at the time that they were lost to follow-up. Patients who died after consent withdrawal were considered as having an overall survival event. Patients who were still alive at the clinical cutoff date for the analysis were censored at the last known date that they were alive; this date was determined by the maximum collection/assessment date from among selected data domains within the clinical database.

Overall rates of overall response, very good partial response or better, and stringent complete response were defined as the percentage of patients in the intention-to-treat population who achieved partial response or better status, very good partial response or better status, and stringent complete response status, respectively, at any time during the study per International

Myeloma Working Group criteria.[2] In addition, the specific response must have been achieved prior to the start of subsequent therapies.

Duration of MRD negativity was defined as the time from the date of first documentation of MRD negativity to the date of first documentation of confirmed disease progression, death due to disease progression, or loss of MRD negativity (at 10^{-4} or higher), whichever occurred first, for patients who achieved MRD negativity in the study. Patients without disease progression or loss of MRD-negative status were censored at the last disease evaluation prior to subsequent therapy or the date of last MRD negativity, whichever was later. Sustained MRD negativity lasting at least 12 months was defined as two consecutive MRD-negative results (10^{-5}) at least 12 months apart, without any MRD-positive results in between.

Disease assessments were performed on day 1 of each cycle in cycles 1 through 6, prior to ASCT, every 4 weeks for the first year of maintenance, and every 8 weeks thereafter until disease progression. MRD was evaluated post consolidation in patients with very good partial response or better; at the time of suspected complete response/stringent complete response; and for patients who achieved complete response/stringent complete response and remained on study, at 12, 18, 24, 30, and 36 months after cycle 1 day 1 and yearly thereafter.

Statistical Analysis

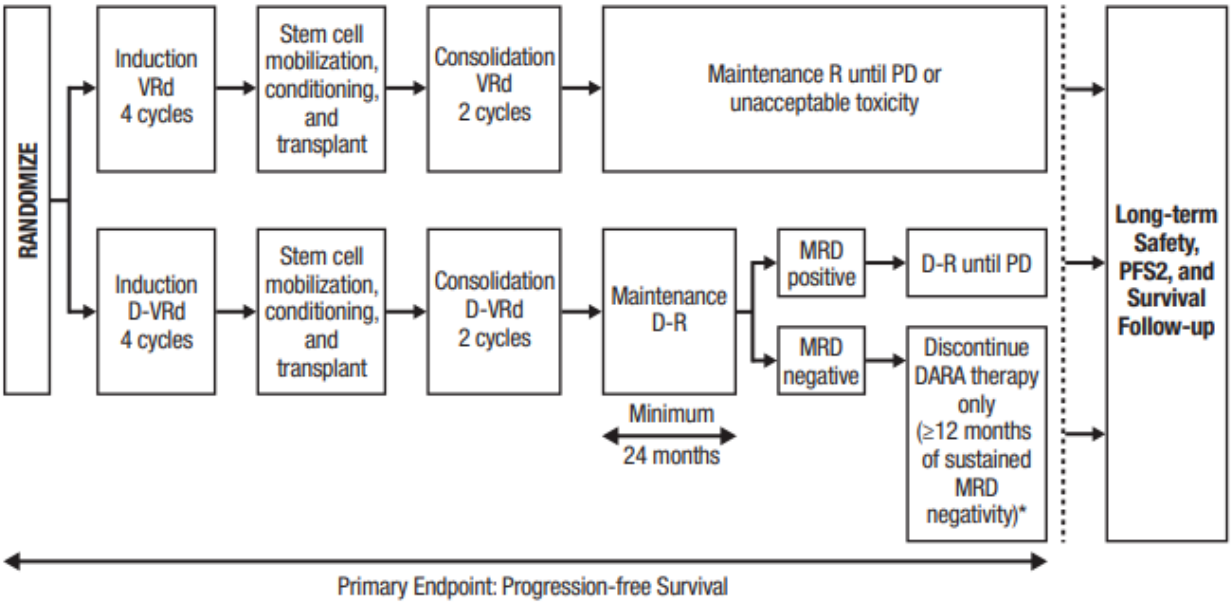
The study design includes two interim analyses and a final analysis for progression-free survival. The first interim analysis was to be performed when approximately 143 progression-free survival events had occurred (corresponding to 50% of the total planned progression-free survival

events); the second interim analysis for progression-free survival will be performed when approximately 185 progression-free survival events have occurred (corresponding to 65% of the total planned progression-free survival events). If the superiority of D-VRd over VRd alone with respect to progression-free survival could be established at the first or second interim analysis, the interim progression-free survival analysis was to serve as the primary progression-free survival analysis, which otherwise was to occur when approximately 285 progression-free survival events had been observed.

A hierarchical testing procedure proposed by Tang and Geller (1999)[3] was used to control overall family-wise type I error for the primary and key secondary endpoints.

The primary endpoint of progression-free survival was tested at the 0.05 significance level (overall); the exact significance level (0.0126) at this interim analysis was determined by the observed number of events (n = 153) per the Hwang-Shih-DeCani alpha spending function,[4] with a gamma parameter = –2.5. If the primary endpoint of progression-free survival was statistically significant, the key secondary endpoints (overall complete response or better rate, overall MRD-negativity rate, and overall survival) were/will be sequentially tested, each with an overall two-sided alpha of 0.05. The overall family-wise type I error rate across the testing of all four hypotheses, over both (interim and final) analyses, was strongly controlled to 5% (two-sided).

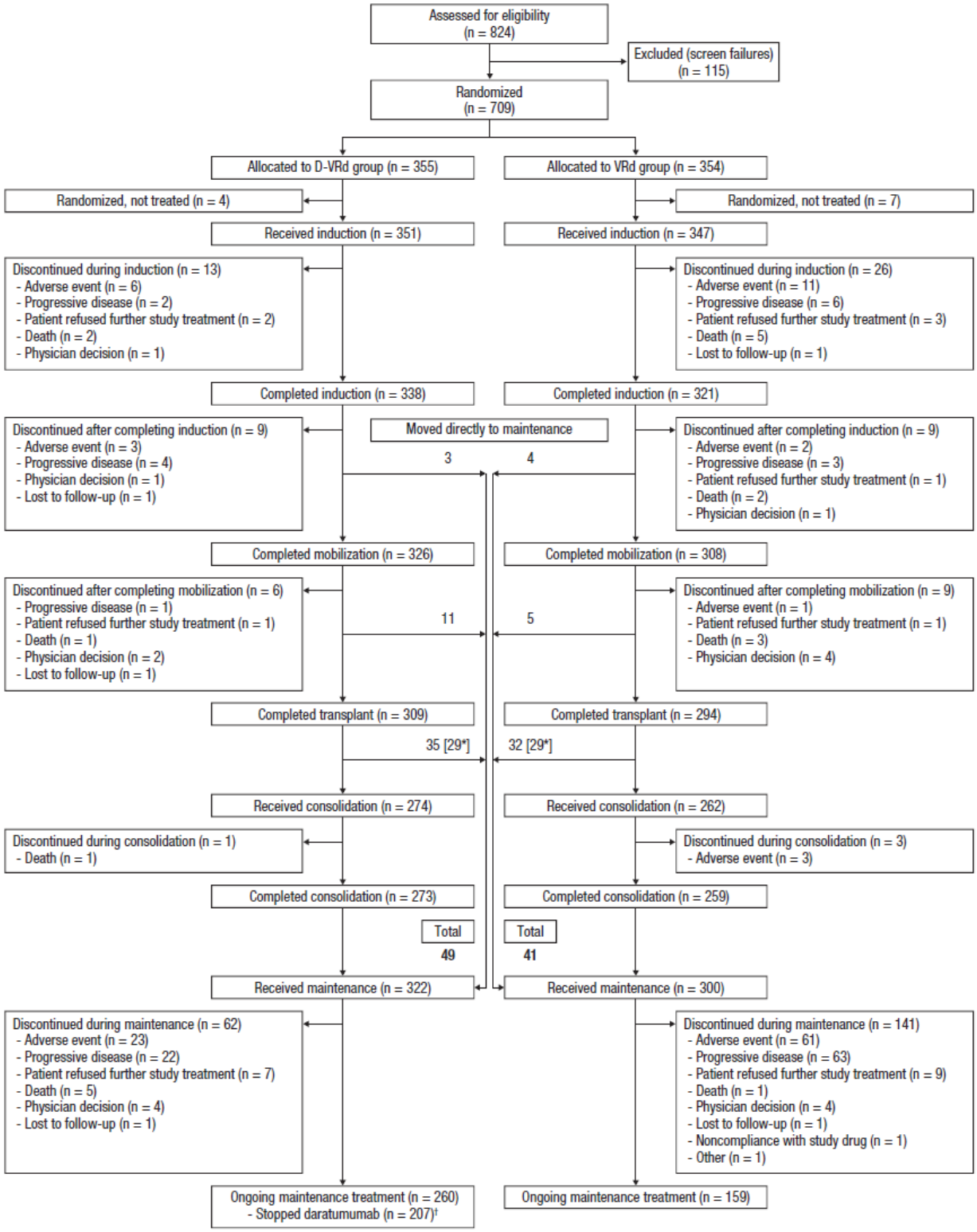
Figure S1. Trial Design.



VRd denotes bortezomib/lenalidomide/dexamethasone. D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. R denotes lenalidomide. PD denotes progressive disease. D-R denotes daratumumab and lenalidomide. MRD denotes minimal residual disease. DARA denotes daratumumab. PFS2 denotes progression-free survival on next line of therapy.

*Restart therapy upon relapse from complete response or loss of MRD status.

Figure S2. CONSORT Patient Flow Diagram.



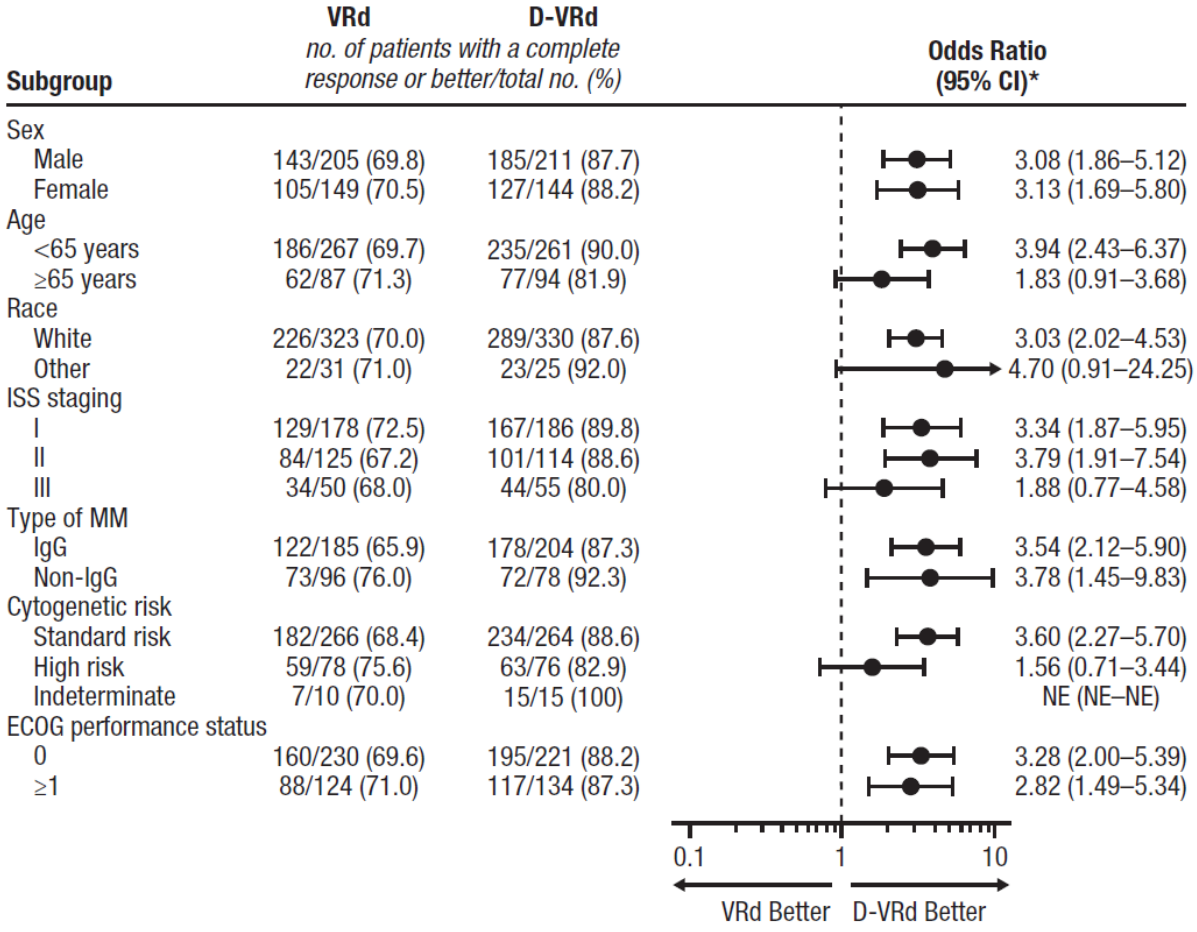
D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. VRd denotes bortezomib/lenalidomide/dexamethasone. COVID-19 denotes coronavirus disease 2019. MRD denotes minimal residual disease.

*Patients who received cycles 5 and 6 consecutive to induction therapy due to the COVID-19 pandemic.

†After at least 24 months of maintenance therapy, daratumumab was discontinued in patients who achieved complete response or better and sustained MRD negativity (at or below a sensitivity threshold of 10^{-5}) for 12 months; patients continued lenalidomide maintenance therapy until disease progression or unacceptable toxicity.

Figure S3. Prespecified Subgroup Analysis of Overall Complete Response or Better Rate.

Shown are the results of an analysis of overall complete response or better rate in prespecified subgroups in the intention-to-treat population. The International Staging System consists of three stages, with higher stages indicating more severe disease: stage I, serum β_2-microglobulin level less than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g or more per deciliter; stage II, neither stage I or III; and stage III, serum β_2-microglobulin level 5.5 mg or more per liter (≥470 nmol per liter). The subgroup analysis for type of MM was performed on data from patients who had measurable disease in serum. Cytogenetic risk was assessed by fluorescence in situ hybridization. High risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

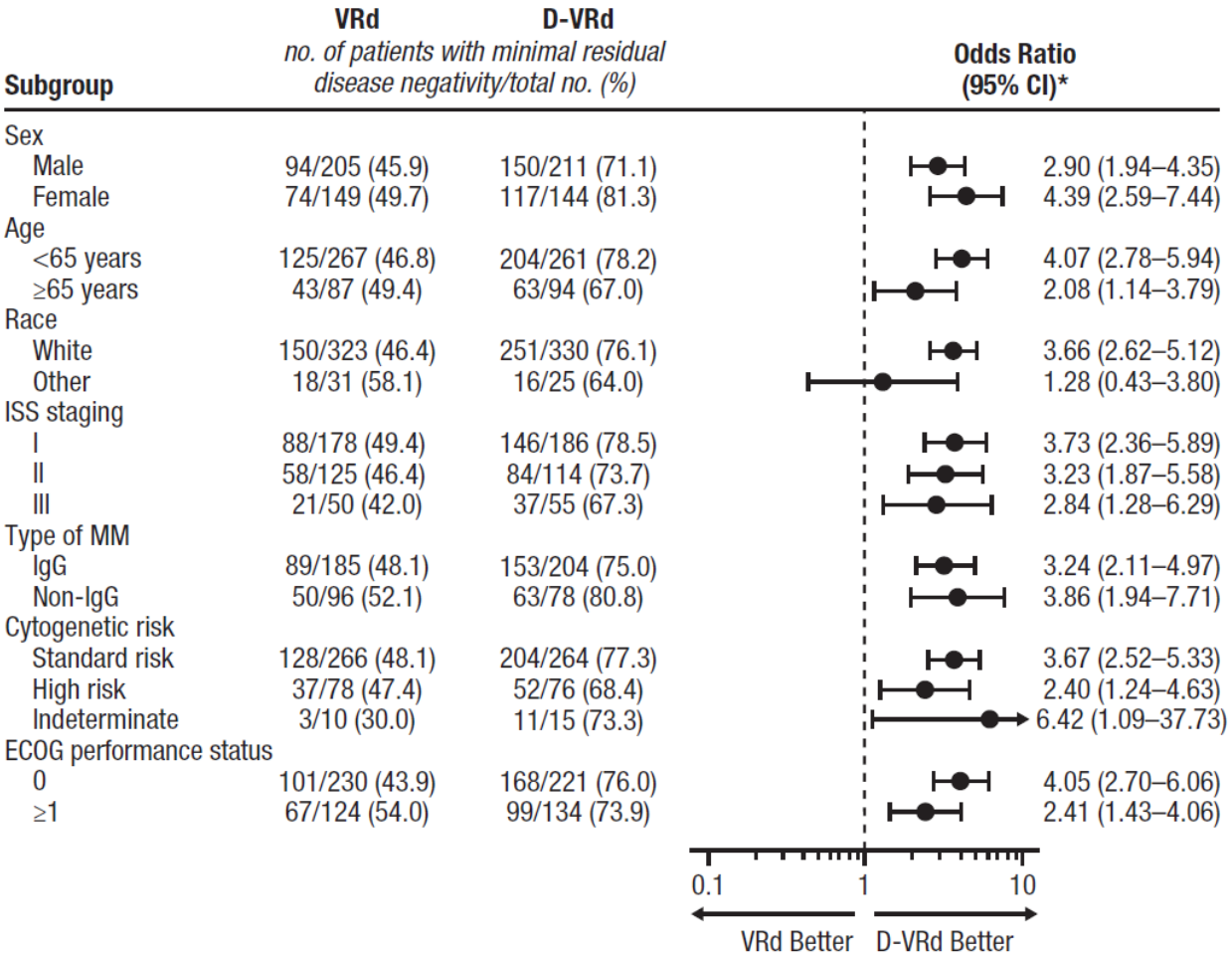


ISS denotes International Staging System. MM denotes multiple myeloma. ECOG denotes Eastern Cooperative Oncology Group. VRd denotes bortezomib/lenalidomide/dexamethasone. D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. CI denotes confidence interval. NE denotes could not be estimated.

*The widths of CIs have not been adjusted for multiplicity and cannot be used to infer treatment effects.

Figure S4. Prespecified Subgroup Analysis of Overall MRD-negativity Rate.

Shown are the results of an analysis of overall MRD-negativity rate in prespecified subgroups in the intention-to-treat population. Overall MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (at or below a sensitivity threshold of 10^{-5}) and a complete response or better at any time during the study after randomization. The International Staging System consists of three stages, with higher stages indicating more severe disease: stage I, serum β_2-microglobulin level less than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g or more per deciliter; stage II, neither stage I or III; and stage III, serum β_2-microglobulin level 5.5 mg or more per liter (≥470 nmol per liter). The subgroup analysis for type of multiple myeloma was performed on data from patients who had measurable disease in serum. Cytogenetic risk was assessed by fluorescence in situ hybridization. High risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

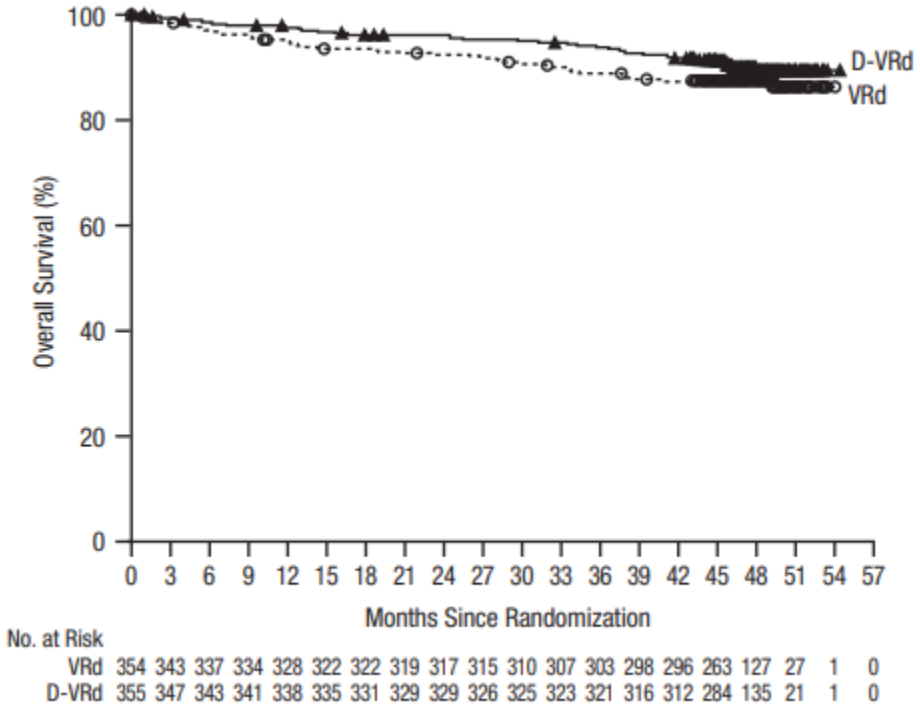


MRD denotes minimal residual disease. ISS denotes International Staging System. MM denotes multiple myeloma. ECOG denotes Eastern Cooperative Oncology Group. VRd denotes bortezomib/lenalidomide/dexamethasone. D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. CI denotes confidence interval.

*The widths of CIs have not been adjusted for multiplicity and cannot be used to infer treatment effects.

Figure S5. Overall Survival.

Shown are the results of the Kaplan–Meier estimates of overall survival among patients in the intention-to-treat population.



D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. VRd denotes bortezomib/lenalidomide/dexamethasone.

Table S1. Representativeness of Study Participants.

Category	Example
Disease, problem, or condition under investigation	Transplant-eligible newly diagnosed multiple myeloma
Special considerations related to	
Sex and gender	Multiple myeloma affects men more than women (3:2 ratio).[5,6]
Age	Multiple myeloma prevalence increases with age. The median age of patients at diagnosis is approximately 66 to 70 years of age; 37% of patients are younger than 65 years of age.[7]
Race or ethnic group	Black patients have a higher incidence of multiple myeloma compared to other ethnicities (more than double the rate in White patients).[8]
Geography	Multiple myeloma incidence and mortality appears highest in Western Europe, the United States, Canada, and Australasia.[9]
Overall representativeness of the study	The patients enrolled in the present study had the expected ratio of men to women. The median age was 60 years (range, 31-70), which aligns with the median age at diagnosis reported in the literature.

	The proportion of Black patients enrolled in the study overall was relatively low (1.3%). The study was conducted in Europe and Australia, which are among the areas with the highest incidence of multiple myeloma.

Table S2. Duration of Treatment and Relative Dose Intensities* During Induction/Consolidation/Maintenance Treatment in the Safety Population.†

	D-VRd (N = 351)				**VRd (N = 347)**		
Median (range) duration of treatment, months	45.7 (0.5–54.3)				42.2 (0.1–53.9)		
Median (range) relative dose intensity, %	**Induction**		**Consolidation**	**Maintenance**	**Induction**	**Consolidation**	**Maintenance**
Bortezomib	(n = 351) 98.0 (25.3–104.8)		(n = 243) 97.8 (12.3–114.2)	NA	(n = 347) 97.8 (40.2–110.4)	(n = 236) 98.2 (9.5–106.0)	NA
Lenalidomide	(n = 351) 100 (28.6–122.2)		(n = 271) 100 (29.5–116.7)	(n = 316) 85.2 (8.5–152.8)	(n = 347) 100 (36.7–105.6)	(n = 260) 100 (23.3–100.0)	(n = 300) 97.1 (39.7–150.4)
Dexamethasone	(n = 351) 100 (20.8–183.3)		(n = 263) 100 (1.6–100.0)	NA	(n = 347) 100 (35.9–121.9)	(n = 250) 100 (10.0–125.0)	NA
	Induction cycles 1-2 (n = 351)	**Induction cycles 3-4 (n = 343)**	**Consolidation (n = 274)**	**Maintenance (n = 322)**			
Daratumumab	100 (50.0–100.4)	100 (25.0–100.0)	100 (50.0–100.0)	100 (67.6–100.0)	NA		

D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. NA denotes not applicable. VRd denotes

bortezomib/lenalidomide/dexamethasone.

*Dose intensity was defined as the ratio of total administered dose to total planned dose.

†The safety population included all patients who received at least one dose of study treatment.

Table S3. List of All Deaths on Study* in the Intention-to-Treat Population.

Treatment Group	Primary Cause	Preferred Term/Description†
VRd	Progressive disease	–
VRd	Adverse event	Acute erythroid leukemia
VRd	Adverse event	Pneumocystis jirovecii pneumonia
VRd	Progressive disease	–
VRd	Other	COVID-19 infection
VRd	Progressive disease	–
VRd	Adverse event	Sepsis
VRd	Other	Multiorgan failure
VRd	Progressive disease	–
VRd	Other	COVID-19
VRd	Progressive disease	–
VRd	Progressive disease	–
VRd	Progressive disease	–
VRd	Adverse event	Pneumonia
VRd	Adverse event	Myocardial infarction
VRd	Adverse event	Acute lymphocytic leukemia
VRd	Adverse event	Myocardial infarction
VRd	Progressive disease	–
VRd	Adverse event	Septic shock

VRd	Progressive disease	–
VRd	Other	Acute myeloid leukemia
VRd	Progressive disease	–
VRd	Progressive disease	–
VRd	Progressive disease	–
VRd	Progressive disease	–
VRd	Adverse event	Septic shock
VRd	Progressive disease	–
VRd	Adverse event	Influenzal pneumonia
VRd	Progressive disease	–
VRd	Adverse event	Sepsis
VRd	Adverse event	Sepsis
VRd	Progressive disease	–
VRd	Progressive disease	–
VRd	Progressive disease	–
VRd	Other	Death due to unknown cause on month October 2022
VRd	Adverse event	Sudden death
VRd	Progressive disease	–
VRd	Adverse event	Acute pulmonary edema
VRd	Adverse event	COVID-19
VRd	Progressive disease	–
VRd	Adverse event	Septic shock

VRd	Adverse event	Lower gastrointestinal hemorrhage
VRd	Adverse event	Cardiac arrest
VRd	Adverse event	Cardiac arrest
D-VRd	Progressive disease	–
D-VRd	Adverse event	Transplantation complication
D-VRd	Adverse event	Pulmonary embolism
D-VRd	Adverse event	Sepsis
D-VRd	Adverse event	COVID-19 pneumonia
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Other	Diffuse large B-cell lymphoma
D-VRd	Adverse event	Myelodysplastic syndrome
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Adverse event	Lower respiratory tract infection
D-VRd	Adverse event	Septic shock
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Adverse event	Acute myocardial infarction

D-VRd	Adverse event	Squamous cell carcinoma
D-VRd	Adverse event	COVID-19
D-VRd	Adverse event	Post-procedural sepsis
D-VRd	Progressive disease	–
D-VRd	Other	Pneumonia
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Progressive disease	–
D-VRd	Other	Fever and intensive care admission after second-line ASCT for multiple myeloma
D-VRd	Adverse event	Death
D-VRd	Progressive disease	–
D-VRd	Adverse event	COVID-19
D-VRd	Adverse event	Sepsis
D-VRd	Progressive disease	–
D-VRd	Adverse event	COVID-19 pneumonia

VRd denotes bortezomib/lenalidomide/dexamethasone. D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. COVID-19 denotes coronavirus disease 2019. ASCT denotes autologous stem cell transplant.

*Up until the clinical cutoff.

[†]As originally entered into the database by the investigator.

Table S4. Serious Adverse Events in the Safety Population.*

	D-VRd (n = 351)	**VRd (n = 347)**
Total no. of patients with serious adverse event – no. (%)	200 (57.0)	171 (49.3)
Serious adverse events occurring in ≥2% of patients in either treatment group – no. (%)		
Infections	123 (35.0)	95 (27.4)
Pneumonia	40 (11.4)	21 (6.1)
COVID-19	13 (3.7)	6 (1.7)
COVID-19 pneumonia	11 (3.1)	5 (1.4)
Lower respiratory tract infection	9 (2.6)	3 (0.9)
Sepsis	7 (2.0)	9 (2.6)
Upper respiratory tract infection	7 (2.0)	8 (2.3)
Febrile neutropenia	16 (4.6)	16 (4.6)
Pyrexia	13 (3.7)	16 (4.6)
Pulmonary embolism	9 (2.6)	5 (1.4)
Atrial fibrillation	9 (2.6)	2 (0.6)
Diarrhea	7 (2.0)	9 (2.6)

COVID-19 denotes coronavirus disease 2019. D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. VRd denotes bortezomib/lenalidomide/ dexamethasone.

*The safety population included patients who received at least one dose of study treatment.

Table S5. Summary of Second Primary Malignancies in the Safety Population.*

	D-VRd (n = 351)	VRd (n = 347)	Total (N = 698)
Total no. of patients with new malignancy – no. (%)	37 (10.5)	25 (7.2)	62 (8.9)
Cancer type/dictionary-derived term – no. (%)			
Cutaneous	20 (5.7)	8 (2.3)	28 (4.0)
Basal cell carcinoma	8 (2.3)	1 (0.3)	9 (1.3)
Squamous cell carcinoma	8 (2.3)	1 (0.3)	9 (1.3)
Malignant melanoma	2 (0.6)	2 (0.6)	4 (0.6)
Squamous cell carcinoma of skin	2 (0.6)	2 (0.6)	4 (0.6)
Bowen's disease	1 (0.3)	1 (0.3)	2 (0.3)
Lentigo maligna	0	1 (0.3)	1 (0.1)
Skin cancer	1 (0.3)	0	1 (0.1)
Superficial spreading melanoma stage unspecified	1 (0.3)	0	1 (0.1)
Hematologic	10 (2.8)	9 (2.6)	19 (2.7)
Myelodysplastic syndrome	4 (1.1)	3 (0.9)	7 (1.0)
Acute myeloid leukemia	3 (0.9)	3 (0.9)	6 (0.9)
Acute lymphocytic leukemia	1 (0.3)	2 (0.6)	3 (0.4)
Acute erythroid leukemia	0	1 (0.3)	1 (0.1)
Angioimmunoblastic T-cell lymphoma	1 (0.3)	0	1 (0.1)
Cutaneous T-cell lymphoma	1 (0.3)	0	1 (0.1)
Diffuse large B-cell lymphoma	1 (0.3)	0	1 (0.1)
Waldenstrom's macroglobulinemia	0	1 (0.3)	1 (0.1)

Noncutaneous	9 (2.6)	8 (2.3)	17 (2.4)
Prostate cancer	1 (0.3)	2 (0.6)	3 (0.4)
Breast cancer	1 (0.3)	1 (0.3)	2 (0.3)
Clear cell renal cell carcinoma	1 (0.3)	1 (0.3)	2 (0.3)
Adenocarcinoma of colon	0	1 (0.3)	1 (0.1)
Breast neoplasm	1 (0.3)	0	1 (0.1)
Colon cancer	1 (0.3)	0	1 (0.1)
Colorectal adenocarcinoma	1 (0.3)	0	1 (0.1)
Gastrointestinal neoplasm	1 (0.3)	0	1 (0.1)
Lung adenocarcinoma	0	1 (0.3)	1 (0.1)
Myxofibrosarcoma	1 (0.3)	0	1 (0.1)
Non–small cell lung cancer stage I	0	1 (0.3)	1 (0.1)
Ovarian cancer	0	1 (0.3)	1 (0.1)
Phaeochromocytoma	0	1 (0.3)	1 (0.1)
Rectal adenocarcinoma	1 (0.3)	0	1 (0.1)
Renal neoplasm	0	1 (0.3)	1 (0.1)
Transitional cell carcinoma	1 (0.3)	0	1 (0.1)

D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. VRd denotes bortezomib/lenalidomide/dexamethasone.

*The safety population included patients who received at least one dose of study treatment.

Table S6. Overview of Adverse Events by Age Subgroup in the Safety Population.*

	D-VRd				VRd			
	<50 y (n = 53)	**50–<65 y (n = 205)**	**≥65 y (n = 93)**	**Total (n = 351)**	**<50 y (n = 53)**	**50–<65 y (n = 207)**	**≥65 y (n = 87)**	**Total (n = 347)**
Treatment-emergent adverse event – no. (%)								
Any grade	52 (98.1)	204 (99.5)	93 (100.0)	349 (99.4)	52 (98.1)	205 (99.0)	87 (100.0)	344 (99.1)
Grade 3	30 (56.6)	116 (56.6)	47 (50.5)	193 (55.0)	29 (54.7)	122 (58.9)	48 (55.2)	199 (57.3)
Grade 4	15 (28.3)	64 (31.2)	38 (40.9)	117 (33.3)	11 (20.8)	46 (22.2)	26 (29.9)	83 (23.9)
Treatment-emergent adverse event leading to treatment discontinuation – no. (%)	2 (3.8)	17 (8.3)	12 (12.9)	31 (8.8)	6 (11.3)	33 (15.9)	35 (40.2)	74 (21.3)
Treatment-emergent adverse event leading to death – no. (%)	0	8 (3.9)	5 (5.4)	13 (3.7)	2 (3.8)	10 (4.8)	4 (4.6)	16 (4.6)

D-VRd denotes subcutaneous daratumumab plus bortezomib/lenalidomide/dexamethasone. VRd denotes bortezomib/lenalidomide/dexamethasone.

*The safety population included patients who received at least one dose of study treatment.

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